

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

MALLINCKRODT LLC, MALLINCKRODT
INC. and DEPOMED, INC.

Plaintiffs,

V.

WATSON LABORATORIES, INC. –
FLORIDA and ACTAVIS LABORATORIES
FL, INC.,

Defendants.

Civil Action No. _____

COMPLAINT

Plaintiffs Mallinckrodt LLC, Mallinckrodt Inc. (collectively and individually, “Mallinckrodt”) and Depomed Inc. (together with Mallinckrodt, collectively “Plaintiffs”), by their undersigned attorneys, for their Complaint against Defendant Watson Laboratories, Inc. – Florida (“Watson”) and Actavis Laboratories FL, Inc. (“Actavis”) (collectively, “Defendants”), herein allege:

NATURE OF ACTION

1. This is an action for patent infringement under the patent laws of the United States, Title 35 of the United States Code, arising from Watson filing an Abbreviated New Drug Application (“ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to market generic versions of Plaintiffs’ pharmaceutical product XARTEMIS™ XR prior to the expiration of United States Patent Nos. 8,597,681 (“the ’681 patent”); 8,658,631 (“the ’631 patent”); 8,741,885 (“the ’885 patent”); 8,980,319 (“the ’319 patent”); 8,992,975 (“the ’975 patent”); 7,976,870 (“the ’870 patent”); and 8,668,929 (“the ’929 patent”).

PARTIES

2. Plaintiff Mallinckrodt LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a place of business at 675 McDonnell Boulevard,

Hazelwood, Missouri 63042-2379.

3. Plaintiff Mallinckrodt Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 675 McDonnell Boulevard, Hazelwood, Missouri 63042-2379.

4. Plaintiff Depomed, Inc. is a corporation organized and existing under the laws of the State of California, having a place of business at 7999 Gateway Blvd., Suite 300, Newark, CA 94560.

5. On information and belief, Defendant Watson Laboratories Inc. – Florida is a company organized and existing under the laws of the State of Florida with a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054. On information and belief, Watson is in the business of selling generic pharmaceutical products, which it distributes in the State of New Jersey and throughout the United States.

6. On information and belief, Defendant Actavis Laboratories FL, Inc., is a company organized and existing under the laws of the State of Florida with a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054. On information and belief, Actavis is in the business of selling generic pharmaceutical products, which it distributes in the State of New Jersey and throughout the United States.

7. On information and belief, Watson has previously submitted to the jurisdiction of this Court and has purposefully availed itself of the jurisdiction of this Court by filing lawsuits and/or asserting counterclaims in lawsuits filed in the United States District Court for the District of New Jersey.

8. On information and belief, Actavis has previously submitted to the jurisdiction of this Court and has purposefully availed itself of the jurisdiction of this Court by filing lawsuits and/or asserting counterclaims in lawsuits filed in the United States District Court for the District

of New Jersey.

JURISDICTION AND VENUE

9. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

10. This Court has personal jurisdiction over Watson by virtue of, *inter alia*, having corporate presence in New Jersey, having conducted business in New Jersey, having availed itself of the rights and benefits of New Jersey law, previously consenting to personal jurisdiction in this Court, availing itself of the jurisdiction of this Court, and having engaged in systemic and continuous contacts with the State of New Jersey.

11. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

XARTEMIS™ XR

12. XARTEMIS™ XR is an extended release tablet for oral administration. XARTEMIS™ XR contains the active ingredients acetaminophen and oxycodone. The recommended dose of XARTEMIS™ XR is one dose every 12 hours without regard to food. XARTEMIS™ XR is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

13. XARTEMIS™ XR combines an opioid analgesic with a non-opioid analgesic agent. XARTEMIS™ XR provides the advantage of additive and synergistic analgesic effects allowing for a lower dose of opioid, fewer side effects, and the ability to treat a broader spectrum of pain or pain states due to the different mechanisms of actions.

14. Previously marketed drug products delivered the combination drugs as an immediate release product.

15. This limitation required the drug product to be administered frequently and/or continuously throughout the day (or night) for continuous pain relief. This frequent and/or

continuous dosing is often inconvenient and difficult to maintain. Regular dosing is, therefore, inconvenient and frequently leads to poor patient compliance – potentially resulting in a dose being taken after pain breaks through, causing unnecessary pain and suffering.

16. During drug development, it was surprisingly discovered that a pharmaceutically acceptable gastric retentive dosage form can be formulated to provide release in the stomach of a combination of a sparingly soluble drug and a highly soluble drug at rates proportional to one another over an extended period of time.

17. In 2008, Mallinckrodt licensed Depomed patents, a patent application, and know-how and sought approval from the FDA to market XARTEMIS™ XR in the United States. The FDA approved Mallinckrodt's New Drug Application No. 204031 ("the XARTEMIS™ XR NDA") for oxycodone hydrochloride and acetaminophen extended-release tablets, under the trade name XARTEMIS™ XR, on March 11, 2014.

18. As a part of the regulatory process for obtaining approval of the XARTEMIS™ XR NDA, Mallinckrodt was required by the FDA to submit a proposed label for the drug. See 21 C.F.R. § 201.56(b). The label for XARTEMIS™ XR instructs physicians and patients, inter alia, about the proper dosage and administration of XARTEMIS™ XR.

19. The label for XARTEMIS™ XR indicates, inter alia, that one dose of XARTEMIS™ XR is recommended twice daily.

20. A physician familiar with the use of extended-release tablets for the management of acute pain such as XARTEMIS™ XR would therefore understand that administration of an opioid analgesic combined with a non-opioid analgesic agent would be subject to the label's instruction to administer a dose twice daily.

21. Plaintiffs have educated prescribing physicians regarding the use of XARTEMIS™ XR. Physicians are informed that the recommended dose of XARTEMIS™ XR

is one dose every 12 hours. Physicians are told that the second dose may be administered as early as 8 hours after the initial dose if patients require analgesia at that time. Subsequent doses are to be administered every 12 hours. Further, on information and belief, it is the standard of care for physicians to treat acute pain in a manner that prevents pain break through. One or more claims of the patents in suit cover the method of treating pain by administering oxycodone hydrochloride and acetaminophen extended-release every 8-12 hours or twice daily.

THE PATENTS-IN-SUIT

22. On December 3, 2013, the United States Patent and Trademark Office issued the '681 patent, entitled "Methods of producing stabilized solid dosage pharmaceutical compositions containing morphinans." The '681 patent was assigned to Mallinckrodt by inventors Jae Han Park, Tiffani Eisenhauer, Anish Dhanarajan, Vishal K. Gupta, and Stephen Overholt. A copy of the '681 patent is attached hereto as Exhibit A.

23. On February 25, 2014, the United States Patent and Trademark Office issued the '631 patent, entitled "Combination composition comprising oxycodone and acetaminophen for rapid onset and extended duration of analgesia." The '631 patent was assigned to Mallinckrodt by inventors Krishna Devarakonda, Michael J. Guiliani, Vishal K. Gupta, Ralph A. Heasley, and Susan Shelby. A copy of the '631 patent is attached hereto as Exhibit B.

24. On June 3, 2014, the United States Patent and Trademark Office issued the '885 patent, entitled "Gastric retentive extended release pharmaceutical compositions." The '885 patent was assigned to Mallinckrodt by inventors Krishna Devarakonda, Michael J. Guiliani, Vishal K. Gupta, Ralph A. Heasley, and Susan Shelby. A copy of the '885 patent is attached hereto as Exhibit C.

25. On March 17, 2015, the United States Patent and Trademark Office issued the '319 patent, entitled "Methods of production stabilized solid dosage pharmaceutical composition

containing morphinans.” The ’319 patent was assigned to Mallinckrodt by inventors Jae Han Park, Tiffani Eisenhauer, Anish Dhanarajan, Vishal Gupta, and Stephen Overholt. A copy of the ’319 patent is attached hereto as Exhibit D.

26. On December 3, 2013, the United States Patent and Trademark Office issued the ’975 patent, entitled “Methods of producing stabilized solid dosage pharmaceutical compositions containing morphinans.” The ’975 patent was assigned to Mallinckrodt by inventors Jae Han Park, Tiffani Eisenhauer, Anish Dhanarajan, Vishal K. Gupta, and Stephen Overholt. A copy of the ’975 patent is attached hereto as Exhibit E.

27. On July 12, 2011, the United States Patent and Trademark Office issued the ’870 patent, entitled “Gastric retentive oral dosage form with restricted drug release in the lower gastrointestinal tract.” The ’870 patent was assigned to Depomed, Inc. by inventors Bret Berner, John W. Shell, and Jenny Louie-Helm. Depomed, Inc. granted Mallinckrodt an exclusive license under the ’870 patent with respect to, inter alia, oxycodone acetaminophen extended release products known as XARTEMIS™ XR. A copy of the ’870 patent is attached hereto as Exhibit F.

28. On March 11, 2014, the United States Patent and Trademark Office issued the ’929 patent, entitled “Gastric retentive extended-release dosage forms comprising combinations of a non-opioid analgesic and an opioid analgesic.” The ’929 patent was assigned to Depomed, Inc. by inventors Chien-Hsuan Han, Sui Yuen Eddie Hou, and Monica L. Reid. Depomed, Inc. granted Mallinckrodt an exclusive license under the ’929 patent with respect to, inter alia, oxycodone acetaminophen extended release products known as XARTEMIS™ XR. A copy of the ’929 patent is attached hereto as Exhibit G.

29. The patents in suit are listed for XARTEMIS™ XR in the Patent and Exclusivity Information Addendum of the FDA’s publication Approved Drug Products with Therapeutic

Equivalence Evaluations (“the Orange Book”). The Patent Use Codes listed in the Orange Book for the XARTEMISTM XR product are “Method of Treating Patients with Gastric Retentive Dosage Form” and “Management of Acute Pain in Patients Requiring Opioid Analgesia.”

WATSON’S ANDA

30. On information and belief, Watson submitted ANDA No. 207113 (“the Watson ANDA”) to the FDA, pursuant to 21 U.S.C. § 355(j), seeking approval to market oxycodone hydrochloride and acetaminophen extended-release tablets before the expiration of the patents in suit expire. The oxycodone hydrochloride and acetaminophen extended-release tablets described in the Watson ANDA are herein referred to as the “Watson Product.”

31. The Watson ANDA refers to and relies upon the XARTEMISTM XR NDA and contains data that, according to Watson, demonstrates the bioequivalence of the Watson Product and XARTEMISTM XR.

32. On or about April 24, 2015, Defendants received Plaintiffs’ letter (the “Watson Notification”) stating that Watson had included a certification in the Watson ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the patents in suit are invalid or will not be infringed by the commercial manufacture, use, or sale of the Watson Product (the “Watson Paragraph IV Certification”).

COUNT I
WATSON’S DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,597,681 UNDER
35 U.S.C. § 271(e)(2)(A)

33. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-32 of this Complaint.

34. Watson has infringed the ’681 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to

the expiration of the '681 patent.

35. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '681 patent.

36. Plaintiffs have no adequate remedy at law.

COUNT II
WATSON'S DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,658,631 UNDER
35 U.S.C. § 271(e)(2)(A)

37. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-36 of this Complaint.

38. Watson has infringed the '631 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to the expiration of the '631 patent.

39. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '631 patent.

40. Plaintiffs have no adequate remedy at law.

COUNT III
WATSON'S DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,741,885 UNDER
35 U.S.C. § 271(e)(2)(A)

41. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-40 of this Complaint.

42. Watson has infringed the '885 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to the expiration of the '885 patent.

43. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined

from infringing the '885 patent.

44. Plaintiffs have no adequate remedy at law.

COUNT IV
WATSON'S DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,980,319 UNDER
35 U.S.C. § 271(e)(2)(A)

45. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-44 of this Complaint.

46. Watson has infringed the '319 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to the expiration of the '319 patent.

47. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '319 patent.

48. Plaintiffs have no adequate remedy at law.

COUNT V
WATSON'S DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,992,975 UNDER
35 U.S.C. § 271(e)(2)(A)

49. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-48 of this Complaint.

50. Watson has infringed the '975 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to the expiration of the '975 patent.

51. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '975 patent.

52. Plaintiffs have no adequate remedy at law.

COUNT VI
WATSON'S DIRECT INFRINGEMENT OF U.S. PATENT NO. 7,976,870 UNDER
35 U.S.C. § 271(e)(2)(A)

53. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-52 of this Complaint.

54. Watson has infringed the '870 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to the expiration of the '870 patent.

55. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '870 patent.

56. Plaintiffs have no adequate remedy at law.

COUNT VII
WATSON'S INDUCEMENT OF INFRINGEMENT OF U.S. PATENT NO. 7,976,870
35 U.S.C. § 271(b)

57. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-56 of this Complaint.

58. On information and belief, approval of the Watson ANDA is substantially likely to result in the commercial use, manufacture, offer for sale and/or sale, or inducement thereof, of a drug product that is marketed and sold for use in a method claimed in one or more claims of the '870 patent, immediately or imminently upon approval of the Watson ANDA.

59. The FDA requires Watson's proposed label for the Watson Product to contain the same prescribing, dosage and administration, and side effect information as found on the XARTEMIS™ XR label. See 21 C.F.R. § 314.94(8)(iv).

60. On information and belief, Watson's proposed label for the Watson Product will instruct patients and physicians to administer one dose of the Watson Product every 12 hours

administered without regard to food. On information and belief, Watson is aware that physician and patients using the Watson Product will do so subject to the label's instruction and administer a dose in a fed mode. On information and belief, Watson will be marketing the Watson Product with specific intent, and/or with desire, to actively induce, aid and abet infringement of the '870 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement of the '870 patent.

61. On information and belief, Watson's generic marketing practices include listing generic products on its website and referring physicians and patients to a corresponding brand name product. On information and belief, Watson intends to do the same for the Watson Product, that is, Watson intends to list its generic product and refer patients to Plaintiffs' product, XARTEMISTM XR. On information and belief, such marketing practices are likely to lead physicians prescribing, and patients using, a generic oxycodone hydrochloride and acetaminophen extended-release tablets product to infer that recommendations regarding the use of XARTEMISTM XR, including recommendations relating to the treatment acute pain from the use of XARTEMISTM XR, also apply to the Watson Product.

62. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '870 patent.

63. Plaintiffs have no adequate remedy at law.

COUNT VIII
WATSON'S DIRECT INFRINGEMENT OF U.S. PATENT NO. 8,668,929 UNDER
35 U.S.C. § 271(e)(2)(A)

64. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-63 of this Complaint.

65. Watson has infringed the '929 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting the Watson ANDA, by which Watson seeks approval from the FDA to engage in the

commercial manufacture, use, offer to sell, sale, or importation of the Watson Product prior to the expiration of the '929 patent.

66. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from infringing the '929 patent.

67. Plaintiffs have no adequate remedy at law.

COUNT IX
WATSON'S INDUCEMENT OF INFRINGEMENT OF U.S. PATENT NO. 8,668,929
UNDER 35 U.S.C. § 271(b)

68. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-67 of this Complaint.

69. On information and belief, approval of the Watson ANDA is substantially likely to result in the commercial use, manufacture, offer for sale and/or sale, or inducement thereof, of a drug product that is marketed and sold for use in a method claimed in one or more claims of the '929 patent, immediately or imminently upon approval of the Watson ANDA.

70. The FDA requires Watson's proposed label for the Watson Product to contain the same prescribing, dosage and administration, and side effect information as found on the XARTEMIS™ XR label. See 21 C.F.R. § 314.94(8)(iv).

71. On information and belief, Watson's proposed label for the Watson Product will instruct patients and physicians to administer one dose of the Watson Product every 12 hours. On information and belief, Watson's proposed label for the Watson Product will inform patients and physicians that the second dose may be administered as early as 8 hours after the initial dose if patients require analgesia at that time, and that subsequent doses are to be administered every 12 hours. On information and belief, Watson is aware that physician and patients using the Watson Product will do so subject to the label's instruction to administer a twice daily dose. On information and belief, Watson will be marketing the Watson Product with specific intent, and/or

with desire, to actively induce, aid and abet infringement of the '929 patent. Watson knows or reasonably should know that its proposed conduct will induce infringement of the '929 patent.

72. On information and belief, Watson's generic marketing practices include listing generic products on its website and referring physicians and patients to a corresponding brand name product. On information and belief, Watson intends to do the same for the Watson Product, that is, Watson intends to list its generic product and refer patients to Plaintiffs' product, XARTEMISTM XR. On information and belief, such marketing practices are likely to lead physicians prescribing, and patients using, a generic oxycodone hydrochloride and acetaminophen extended-release tablets product to infer that recommendations regarding the use of XARTEMISTM XR, including recommendations relating to the treatment of acute pain with XARTEMISTM XR, also apply to the Watson Product.

73. On information and belief, the acts of infringement alleged above are and have been deliberate and willful.

74. Plaintiffs will be substantially and irreparably harmed if Watson is not enjoined from inducing infringement of the '929 patent.

75. Plaintiffs have no adequate remedy at law.

COUNT X
EXCEPTIONAL CASE WITH RESPECT TO WATSON UNDER 35 U.S.C. § 285

76. Plaintiffs reallege and incorporate by reference the allegations of paragraphs 1-75 of this Complaint.

77. This case is an exceptional one, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285 in light of Watson's conduct.

PRAYER FOR RELIEF

WHEREFORE, Mallinckrodt Inc., Mallinckrodt LLC, and Depomed, Inc. pray for a

judgment in their favor and against Defendant Watson Pharmaceuticals LLC and respectfully request the following relief:

A. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 8,597,681;

B. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 8,658,631;

C. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 8,741,885;

D. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 8,980,319;

E. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 8,992,975;

F. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 7,976,870;

G. A judgment declaring that Watson has directly infringed and will induce infringement of U.S. Patent No. 8,668,929;

H. A judgment pursuant to 35 U.S.C. § 271(e)(4)(B) preliminarily and permanently enjoining Watson, its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from manufacturing, using, offering to sell, or selling the Watson Product within the United States, or importing the Watson Product into the United States, prior to the expiration date of the patents in suit;

I. A judgment ordering that pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 207113 under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration date of the patents in suit,

including any exclusivities and extensions;

J. If Watson commercially manufactures, uses, offers to sell, or sells the Watson Product within the United States, or imports the Watson Product into the United States, prior to the expiration of the patents in suit, including any exclusivities and extensions, a judgment awarding Plaintiffs monetary relief together with interest;

K. Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285.

L. Costs and expenses in this action; and

M. Such other relief as the Court deems just and proper.

LITE DEPALMA GREENBERG, LLC

Dated: June 5, 2015

s/Michael E. Patunas

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EXHIBIT A

US008597681B2

(12) **United States Patent**
Park et al.(10) **Patent No.:** **US 8,597,681 B2**
(45) **Date of Patent:** **Dec. 3, 2013**(54) **METHODS OF PRODUCING STABILIZED
SOLID DOSAGE PHARMACEUTICAL
COMPOSITIONS CONTAINING
MORPHINANS**(75) Inventors: **Jaе Han Park**, Olivette, MO (US);
Tiffani Eisenhauer, Columbia, IL (US);
Anish Dhanarajan, Metuchen, NJ (US);
Vishal K. Gupta, Hillsborough, NJ
(US); **Stephen Overholt**, Middlesex, NJ
(US)(73) Assignee: **Mallinckrodt LLC**, Hazelwood, MO
(US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **13/166,770**(22) Filed: **Jun. 22, 2011**(65) **Prior Publication Data**

US 2011/0287095 A1 Nov. 24, 2011

Related U.S. Application Data(63) Continuation-in-part of application No. 12/973,962,
filed on Dec. 21, 2010.(60) Provisional application No. 61/284,651, filed on Dec.
22, 2009.(51) **Int. Cl.****A61K 9/24** (2006.01)**A61K 9/16** (2006.01)**A61K 9/22** (2006.01)**A61K 9/50** (2006.01)**A61K 31/46** (2006.01)**A61K 31/485** (2006.01)(52) **U.S. Cl.**USPC **424/472**; 424/468; 424/490; 514/282;
514/289(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**

4,713,243 A 12/1987 Schiraldi et al.
4,851,226 A 7/1989 Julian et al.
4,894,236 A 1/1990 Jang
4,996,058 A 2/1991 Sinnreich
5,075,114 A 12/1991 Roche
5,266,331 A 11/1993 Oshlack et al.
5,336,691 A 8/1994 Raffa et al.
5,478,577 A 12/1995 Sackler et al.
5,508,042 A 4/1996 Oshlack et al.
5,549,912 A 8/1996 Oshlack et al.
5,582,837 A 12/1996 Shell
5,626,874 A 5/1997 Conte et al.
5,656,295 A 8/1997 Oshlack et al.
5,672,360 A 9/1997 Sackler et al.
5,783,212 A 7/1998 Fassih et al.

5,866,161 A 2/1999 Childers et al.
5,876,759 A 3/1999 Gowan, Jr.
5,891,471 A 4/1999 Miller et al.
5,945,123 A 8/1999 Hermelin
5,945,125 A 8/1999 Kim
5,958,459 A 9/1999 Chasin et al.
5,965,161 A 10/1999 Oshlack et al.
5,965,163 A 10/1999 Miller et al.
5,965,167 A 10/1999 Sanghvi et al.
5,968,551 A 10/1999 Oshlack et al.
5,972,389 A 10/1999 Shell et al.
5,980,882 A 11/1999 Eichman
6,024,982 A 2/2000 Oshlack et al.
6,068,855 A 5/2000 Leslie et al.
6,071,208 A 6/2000 Koivunen
6,103,219 A 8/2000 Sherwood et al.
6,103,261 A 8/2000 Chasin et al.
6,126,969 A 10/2000 Shah et al.
6,143,322 A 11/2000 Sackler et al.
6,210,714 B1 4/2001 Oshlack et al.
6,245,357 B1 6/2001 Edgren et al.
6,254,887 B1 7/2001 Miller et al.
6,340,475 B2 1/2002 Shell et al.
6,348,216 B1 * 2/2002 Kushla et al. 424/465
6,372,254 B1 4/2002 Ting et al.
6,375,957 B1 4/2002 Kaiko et al.
6,387,404 B2 5/2002 Oshlack et al.
6,488,962 B1 12/2002 Berner et al.
6,488,963 B1 12/2002 McGinity et al.
6,500,459 B1 12/2002 Chhabra et al.
6,599,529 B1 7/2003 Skinhoj et al.
6,635,280 B2 10/2003 Shell et al.
6,667,060 B1 12/2003 Vandecruys et al.
6,682,759 B2 1/2004 Lim et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP 0159852 A2 * 10/1985
EP 1140026 6/2000

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 13/360,595, filed Jan. 27, 2012, Hien-Hsuan Han et al.
Banfai B. Ganzler K, Kemeny S. Content uniformity and assay
requirements in current regulations. J Chromatogr A. Jul. 13,
2007;1156(1-2):206-12. Epub Nov. 15, 2006.
Zhu Y, Shah NH Malick AW, Infeld MH, McGinity JW. Solid-state
plasticization of an acrylic polymer with chlorpheniramine maleate
and triethyl citrate. Int J Pharm. Jul. 25, 2002; 241(2):301-10.
Nimmo, W.S. et al., "Inhibition of Gastric Emptying and Drug
Absorption by Narcotic Analgesics", Br. J. Clin. Pharmac., 2:509-
513 (1975).

(Continued)

Primary Examiner — Frederick Krass*Assistant Examiner* — Michael P Cohen(74) *Attorney, Agent, or Firm* — Mayer Brown LLP(57) **ABSTRACT**

Methods for producing stabilized solid dosage form pharma-
ceutical compositions are provided. In particular, methods for
preparing protected granules containing morphinans, and
solid dosage form pharmaceutical compositions produced
using the morphinan-protected granules are provided.

39 Claims, No Drawings

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(56)

References Cited

U.S. PATENT DOCUMENTS

6,696,066	B2	2/2004	Kaiko et al.	2008/0020039	A1	1/2008	Parikh et al.
6,706,281	B2	3/2004	Oshlack et al.	2008/0031901	A1	2/2008	Qiu et al.
6,723,340	B2	4/2004	Gusler et al.	2008/0031963	A1	2/2008	Sackler et al.
6,730,321	B2	5/2004	Ting et al.	2008/0044482	A1	2/2008	Oshlack et al.
6,733,783	B2	5/2004	Oshlack et al.	2008/0057122	A1	3/2008	Toney-Parker et al.
6,797,283	B1	9/2004	Edgren et al.	2008/0113025	A1	5/2008	Devane et al.
6,852,336	B2	2/2005	Hunter et al.	2008/0132532	A1	6/2008	Wright et al.
6,902,742	B2	6/2005	Devane et al.	2008/0138422	A1	6/2008	Staniforth
7,074,430	B2	7/2006	Miller et al.	2008/0220062	A1	9/2008	Ashton
7,201,920	B2	4/2007	Kumar et al.	2009/0022798	A1	1/2009	Rosenberg et al.
7,374,781	B2	5/2008	Zhang et al.	2009/0028941	A1	1/2009	Cowles et al.
7,405,238	B2	7/2008	Markey et al.	2009/0068269	A1	3/2009	Oshlack et al.
7,413,751	B2	8/2008	Devane et al.	2009/0081290	A1	3/2009	McKenna et al.
7,438,927	B2	10/2008	Berner et al.	2009/0149479	A1	6/2009	Jenkins et al.
7,514,100	B2	4/2009	Oshlack et al.	2009/0155357	A1	6/2009	Muhuri
7,674,799	B2	3/2010	Chapman et al.	2009/0175937	A1	7/2009	Rahmouni et al.
7,683,072	B2	3/2010	Chapman et al.	2009/0202629	A1	8/2009	Oshlack et al.
7,691,873	B2	4/2010	Duncalf et al.	2009/0304793	A1	12/2009	Boehm
7,776,314	B2	8/2010	Bartholomaeus et al.	2009/0306119	A1	12/2009	Keane
7,846,476	B2	12/2010	Oshlack et al.	2009/0311320	A1	12/2009	Oury et al.
7,897,172	B2	3/2011	Qasem et al.	2009/0317355	A1	12/2009	Roth et al.
7,939,543	B2	5/2011	Kupper	2009/0324714	A1	12/2009	Liu et al.
7,943,170	B2	5/2011	Chan et al.	2010/0010030	A1	1/2010	Jain et al.
7,976,870	B2	7/2011	Berner et al.	2010/0015222	A1	1/2010	Han et al.
8,075,872	B2	12/2011	Arkenau-Maric et al.	2010/0034876	A1	2/2010	Oshlack et al.
2001/0008639	A1	7/2001	Oshlack et al.	2010/0040681	A1	2/2010	Park et al.
2002/0018810	A1	2/2002	Oshlack et al.	2010/0092570	A1	4/2010	Oshlack et al.
2002/0058050	A1	5/2002	Sackler et al.	2010/0168148	A1	7/2010	Wright et al.
2003/0035837	A1	2/2003	Sackler et al.	2010/0172974	A1	7/2010	Oshlack et al.
2003/0044466	A1	3/2003	Markey et al.	2010/0172989	A1	7/2010	Roth et al.
2003/0091635	A1	5/2003	Baichwal et al.	2010/0196425	A1	8/2010	Cruz et al.
2003/0092724	A1*	5/2003	Kao et al. 514/282	2010/0196471	A1	8/2010	Jain et al.
2003/0099704	A1	5/2003	Oshlack et al.	2010/0196474	A1	8/2010	Han et al.
2003/0104062	A1	6/2003	Berner et al.	2010/0216829	A2	8/2010	Kumar et al.
2003/0180361	A1*	9/2003	Oshlack et al. 424/469	2010/0221293	A1	9/2010	Cruz et al.
2004/0096500	A1	5/2004	Oshlack et al.	2010/0239662	A1	9/2010	Rahmouni et al.
2004/0105887	A1	6/2004	Oshlack et al.	2010/0260833	A1	10/2010	Bartholomaeus et al.
2004/0131671	A1	7/2004	Zhang et al.	2011/0020451	A1	1/2011	Bartholomaeus et al.
2004/0156899	A1	8/2004	Louie-Helm et al.	2011/0038927	A1	2/2011	Oshlack et al.
2004/0224020	A1*	11/2004	Schoenhard 424/471	2011/0038930	A1	2/2011	Barnscheid et al.
2005/0013863	A1	1/2005	Lim et al.	2011/0052685	A1	3/2011	Hou et al.
2005/0020613	A1	1/2005	Boehm et al.	2011/0077238	A1	3/2011	Leech et al.
2005/0031546	A1	2/2005	Bartholomaeus et al.	2011/0117196	A1	5/2011	Gordon
2005/0089570	A1	4/2005	Cruz et al.	2011/0118189	A1	5/2011	Farr et al.
2005/0106249	A1	5/2005	Hwang et al.	2011/0129507	A1	6/2011	Cruz
2005/0112195	A1	5/2005	Cruz et al.	2011/0150969	A1	6/2011	Shah et al.
2005/0158382	A1	7/2005	Cruz et al.	2011/0150970	A1	6/2011	Shah et al.
2005/0165038	A1	7/2005	Gordon	2011/0150971	A1	6/2011	Shah et al.
2005/0214251	A1*	9/2005	Pohl et al. 424/85.1	2011/0150990	A1	6/2011	Shah et al.
2005/0232987	A1	10/2005	Srinivasan et al.	2011/0150991	A1	6/2011	Shah et al.
2005/0266032	A1	12/2005	Srinivasan et al.	2011/0159046	A1	6/2011	Cruz
2006/0002860	A1	1/2006	Bartholomaeus et al.	2011/0166171	A1	7/2011	Qiu et al.
2006/0057210	A1	3/2006	Oshlack et al.	2011/0177168	A1	7/2011	Chan et al.
2006/0099255	A1	5/2006	Oshlack et al.	2011/0195116	A1	8/2011	Hobbs et al.
2006/0165791	A1	7/2006	Oshlack et al.	2011/0195989	A1	8/2011	Rudnic et al.
2006/0193782	A1	8/2006	Bartholomaeus et al.	2011/0207762	A1	8/2011	Chapman et al.
2006/0205752	A1	9/2006	Whitehead	2011/0212173	A1	9/2011	Young et al.
2006/0240105	A1	10/2006	Devane et al.	2011/0229526	A1	9/2011	Rosenberg et al.
2006/0251721	A1	11/2006	Cruz et al.	2011/0229533	A1	9/2011	Edgren et al.
2006/0263436	A1	11/2006	Baert et al.	2011/0262532	A1	10/2011	Oshlack et al.
2006/0269604	A1	11/2006	Sackler et al.	2011/0301129	A1	12/2011	Berner et al.
2006/0292214	A1	12/2006	Jenkins et al.	2011/0318392	A1	12/2011	Cruz et al.
2007/0020335	A1	1/2007	Chen et al.	2012/0321713	A1	12/2012	Han et al.
2007/0048228	A1	3/2007	Arkenau-Maric et al.				
2007/0059359	A1	3/2007	Backensfeld et al.				
2007/0128279	A1	6/2007	Edgren et al.				
2007/0183980	A1	8/2007	Arkenau-Maric et al.				
2007/0184112	A1	8/2007	Wong et al.				
2007/0190142	A1	8/2007	Breitenbach et al.				
2007/0207200	A1	9/2007	Plachetka et al.				
2007/0237833	A1	10/2007	Sackler et al.				
2007/0259033	A1	11/2007	Cruz				
2007/0259045	A1	11/2007	Mannion et al.				
2007/0275065	A1	11/2007	Oshlack et al.				
2007/0281018	A1	12/2007	Qiu et al.				

FOREIGN PATENT DOCUMENTS

WO	9718814	5/1997
WO	9855107	12/1998
WO	03024426	3/2003
WO	2005013863	2/2005
WO	2005030182	4/2005
WO	2006022759	3/2006
WO	2006071208	7/2006
WO	2008015221	2/2008
WO	2009049405	4/2009
WO	2009076764	6/2009
WO	2009114648	9/2009
WO	2009135846	11/2009
WO	2010032128	3/2010

US 8,597,681 B2

Page 3

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2010069050	6/2010
WO	2010078486	7/2010
WO	2010141505	12/2010
WO	2011009603	1/2011
WO	2011009604	1/2011
WO	2011068723	6/2011
WO	2011077451	6/2011
WO	2011106416	9/2011
WO	2012007159	1/2012

OTHER PUBLICATIONS

Altaf S A et al., "Bead Compacts II. Evaluation of Rapidly Disintegrating Nonsegregating Compressed Bead Formulations"; Drug Development and Industrial Pharmacy, New York, NY, US, vol. 25, No. 5, May 1, 1999; pp. 635-642.

International Search Report from Application No. PCT/US2010/061400 with a mailing date of Nov. 25, 2011.

Endo Pharmaceuticals Package Insert for Percocet(Oxycodone and Acetaminophen Tablets, USP); pp. 1-17.

www.fda.gov/Drugs/DrugSafety/ucm239821.htm; U.S. Department of Health & Human Services; FDA Drugs Safety Communication: Prescription Acetaminophen Products to be Limited to 325mg per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure; pp. 1-5.

Tylenol Professional Product Information(2010); McNeil Consumer Healthcare; pp. 1-59.

Oxycontin Description and Patient Information; pp. 1-32.

Cooperman et al.; "A Novel Extended-Release Formulation of Oxycodone/Acetaminophen with Abuse Deterrent Properties"; Abstract; 2pgs.

Brzezniacka et al. "Dynamics of Glutathione Levels in Liver and Indicatory Enzymes in Serum in Acetaminophen Intoxication in Mice" (1989) Polish Journal of Occupational Medicine, vol. 2, No. 1, pp. 15-22.

Gammaitoni et al. "Randomized, Double-Blind, Placebo-Controlled Comparison of the Analgesic Efficacy of Oxycodone 10 mg/Acetaminophen 325 mg versus Controlled-Release Oxycodone 20 mg in Postsurgical Pain", (2003), J. Clin. Pharmacol. 43: pp. 296-304.

Moller et al. "Time to Onset of Analgesia and Analgesic Efficacy of Effervescent Acetaminophen," (2000); J. Clin. Pharmacol. 40: 370-378.

Nielsen et al. "Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol", (1992), Eur. J. Clin Pharmacol 42: 261-264.

James et al., "Acetaminophen-Induced Hepatotoxicity", The American Society for Pharmacology and Experimental Therapeutics, (2003), vol. 31, No. 12, pp. 1499-1506.

Mirochnitchenko et al. "Acetaminophen Toxicity", The American Society for Biochemistry and Molecular Biology, Inc., (1999), vol. 274, No. 15, pp. 10349-10355.

Dart et al. "Acetaminophen Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management", (2006), Clinical Toxicology; 44: pp. 1-18.

Bolesta et al. "Hepatotoxicity Associated with Chronic Acetaminophen Administration in Patients without Risk Factors", (2002), The Annals of Pharmacotherapy; Feb. 2002, Vol. 36, pp. 331-333.

Rinaldi et al. "Minireview Reactive Intermediates and the Dynamics of Glutathione Transferases" (2002); The American Society for Pharmacology and Experimental Therapeutics; 30:pp. 1053-1058.

Rumack et al. "Acetaminophen Hepatotoxicity: The First 35 Years", Clinical Toxicology, (2002); 40(1), 3-20.

Bartels et al., "Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial"; (2008); Clinical Toxicology; 46; 243-249.

Corcoran et al. "Role of Glutathione in Prevention of Acetaminophen-Induced Hepatotoxicity by N-Acetyl-L-Cysteine in

Vivo: Studies with N-Acetyl-D-Cysteine in Mice"; The Journal of Pharmacology and Experimental Therapeutics; (1986); vol. 238, No. 1; pp. 54-61.

Davis et al. "Species Differences in Hepatic Glutathione Depletion, Covalent Binding and Hepatic Necrosis after Acetaminophen", Life Sciences, vol. 14, pp. 2099-2109.

Mitchell et al. "Acetaminophen-Induced Hepatic Necrosis. IV. Protective Role of Glutathione", The Journal of Pharmacology and Experimental Therapeutics; (1973), vol. 187, No. 1, pp. 211-217.

Kaplowitz et al. "Drug-Induced Liver Disease" (2003); Marcel Dekker, pp. 287-325 and pp. 345-375.

Skoglund et al. "Efficacy of paracetamol-esterified methionine versus cysteine or methionine on paracetamol-induced hepatic GSH depletion and plasma AIAT level in mice", Biochem Pharmacol 35; 3071-3075, (1986).

Khosla et al. "The effect of tablet size on the gastric emptying of non-disintegrating tablets" (1990), International Journal of Pharmaceutics, 62, R9-R11.

Khosla et al. Gastrointestinal transit of non-disintegrating tablets in fed subjects (1989), International Journal of Pharmaceutics, 53, 107-117.

Khosla et al. "The gastrointestinal transit of a controlled release formulation of indomethacin", (1990), International Journal of Pharmaceutics, 60, 191-196.

Foremost NF Flo Lactose, "A spray-dried mixture of crystalline and amorphous lactose", Foremost Farms USA, 1pg., Online Article downloaded from the site: http://www.foremostfarms.com/Commercial/pdfs/Specifications/TDS_NF_Lactose_316.pdf, Document created on Jan. 28, 2010.

Freed et al. "pH control on nucleophilic/electrophilic oxidation", Int. J. Pharm., vol. 357, pp. 180-188 (2008).

International Search Report from related PCT Patent application No. PCT/US2009/036864 mailed Aug. 31, 2009, application now published as PCT Publication No. WO2009/114648 on Sep. 17, 2009. Lab Basics Technical Library, Particle Size Conversion Table, Sigma-Aldrich, 3 pgs., Online Article downloaded from the site: <http://www.sigmaaldrich.com/chemistry/stockroom-reagents/learning-center/technical-library/particle-size-conversion.printerview.html> on Apr. 17, 2012.

Polyox Water-Soluble Resins, Technical Data, "Degradation of water-soluble resins", Form 326-00027-1002AMS (2002).

Polyox Water-Soluble Resins, Technical Data, "Water-soluble resin storage stability", Form 326-00044-0704MAB (2004).

Waterman et al., "Stabilization of pharmaceuticals to oxidative degradation", Pharm. Dev. Tech., vol. 7, No. 1, pp. 1-32 (2002).

Zhang et al., "Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release", Pharm. Dev. Tech., vol. 6, No. 2, pp. 131-144 (2001).

Meert et al., A preclinical comparison between different opioids: antinociceptive versus adverse effects; Pharmacology, Biochemistry & Behavior; 80(2):309-26, Feb. 2005.

Doteuchi et al., "Pharmacological Studies of Oxycodone Hydrochloride 1. Antinociceptive Effect and General Pharmacology"; Oyo Yakuri. 49(3); 1995; 257-273.

Talukder et al.; "Gastroretentive Delivery Systems: A Mini Review"; Drug Development and Industrial Pharmacy; 2004; pp. 1019-1028; vol. 30, No. 10.

Hou et al.; "Gastric Retentive Dosage Forms: A Review"; Critical Review in Therapeutic Drug Carrier Systems; 2003; pp. 462-497; 20(6).

Streubel et al. "Drug delivery to the upper small intestine window using gastroretentive technologies"; ScienceDirect; 2006; pp. 501-508; 6.

Streubel et al. "Gastroretentive drug delivery systems"; Expert Opin. Drug Deliv.; 2006; pp. 217-233; 3(2).

Moes, A.J.; "Gastroretentive Dosage Forms"; Critical Reviews in Therapeutic Drug Carrier Systems; 1993; pp. 143-195; 10(2).

Davis, Stanley, S.; "Formulation strategies for absorption windows"; DDT; Feb. 2005; pp. 249-257; vol. 10, No. 4.

Bardonnet et al.; "Gastroretentive dosage forms: Overview and special case of *Helicobacter pylori*"; Journal of Controlled Release; 2006; pp. 1-18; 111.

US 8,597,681 B2

Page 4

(56)

References Cited**OTHER PUBLICATIONS**

Freed et al., "pH control of nucleophilic/electrophilic oxidation", *Int. J. of Pharm.*, 357, 2008, pp. 180-188.

Waterman et al., "Stabilization of Pharmaceuticals to Oxidative Degradation", *Pharm. Dev. Tech.*, 7(1), 2002, pp. 1-32.

"Degradation of Water-Soluble Resins", Technical Data, Polyox Water-Soluble Resins, Form 326-00027-1002AMS, 2002.

"Water-Soluble Resin Storage Stability", Technical Data, polyox Water-Soluble Resins, Form No. 326-00044-0704MAB, 2004.

Miller et al., "Physical and chemical characteristics of some high purity magnesium stearate and palmitate powders"; *Intl Journal of Pharmaceutics*, 23 (1985), 55-67.

Kim, Chong-Ju, "Effects of Drug Solubility, Drug Loading, and Polymer Molecular Weight on Drug Release from Polyox Tablets", *Drug Development and Industrial Pharmacy*; 24(7), (1998), 645-651.

Waterman, Kenneth, C., "A Critical Review of Gastric Retentive Controlled Drug Delivery", *Pharmaceutical Development and Technology*, 12:1-10, (2007).

Arora et al., "Floating Drug Delivery Systems: A Review", *AAPS PharmSciTech* (2005), 6(3) Article 47 E372-390.

Klausner et al., "Novel Gastrorotative Dosage Forms: Evaluation of Gastrorotativity and Its Effect on Levodopa Absorption in Humans"; *Pharmaceutical Research*, Vol. 20, No. 9, Sep. 2003; pp. 1466-1473.

Klausner, et al., "Novel levodopa gastrorotative dosage form: in-vivo evaluation in dogs", *Journal of Controlled Release* 88 (2003) 117-126.

Aulton M. E. "Aulton's Pharmaceutics: The Design and Manufacture of Medicines," Elsevier Limited, Oxford, Third Edition, 2007, pp. 270-278.

Prinderre et al., "Advances in Gastro Retentive Drug-Delivery Systems," *Expert Opin. Drug. Deliv.*, 8(9), p. 1189-1203 (Sep. 2011).

Berner et al., "Case Studies in Swelling Polymeric Gastric Retentive Tablets," *Expert Opin. Drug. Deliv.*, 3(4), p. 541-548 (Jul. 2006).

Gralise Prescribing Information, 24 pages.

Glumetza Prescribing Information, 10 pages.

Tylenol® Professional Product Information, 62 pages.

Patterson Kelley Chemical and Process Equipment Division; "P-K Liquid-Solids Blender Granulates Tablet Formulations in a Single Step"; *At Ortho Pharmaceutical Corp.*; vol. 53, No. 4, Apr. 1961 41A.

Lieberman et al. editors; "Pharmaceutical Dosage forms—tablets"; *Library of Congress Cataloging*; 1989 Marcel Dekker, Inc.; 2nd ed.

* cited by examiner

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METHODS OF PRODUCING STABILIZED SOLID DOSAGE PHARMACEUTICAL COMPOSITIONS CONTAINING MORPHINANS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 12/973,962, filed Dec. 21, 2010, which claims priority to U.S. Provisional Application No. 61/284,651 filed on Dec. 22, 2009, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to methods of producing stabilized solid dosage forms of morphinan pharmaceutical compositions. In particular, the present invention relates to methods of preparing morphinan-protected granules that may be incorporated into solid dosage forms of morphinan pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Minimizing the degradation of active pharmaceutical ingredients (APIs) in pharmaceutical compositions is an ongoing challenge in research and development. Degradation may occur from the physical or chemical instability of the API with incompatible pharmaceutical carriers in a pharmaceutical composition, or by reactions of the API with headspace oxygen or residual water in a composition.

Oxidation is a common mechanism of API degradation in pharmaceutical compositions. The process of oxidative degradation may occur via various mechanisms such as autooxidation, nucleophilic addition, electrophilic addition, or electron transfer. Regardless of the mechanism, degradant compounds formed by the degradation of an API in a pharmaceutical composition may impart potentially harmful properties to the composition.

If degradants are present in a pharmaceutical composition above the levels prescribed by ICH Guidelines Q3A and Q3B, the degradants must undergo a qualification procedure as part of the approval process required before the use and sale of the composition is allowed. Qualification of impurities typically involves costly studies using multiple animal models, and introduces considerable risk into the development process. If degradants of a pharmaceutical composition are found to be carcinogenic or teratogenic, the composition will not gain FDA approval, diminishing the opportunity for commercialization of the API.

As a result, the process of selecting functional carriers for a pharmaceutical composition is particularly challenging. A functional pharmaceutical carrier is typically selected primarily to impart desired performance characteristics to the composition such as an extended release profile. In addition, it is desirable to select functional carriers that are chemically compatible with the API in the composition. In certain compositions, it may be necessary to incorporate functional carriers that may be incompatible with the API in order to achieve a desired performance of the API in the body. In this situation, identifying an effective means to prevent the degradation of the API is an essential part of the development of a successful therapeutic composition.

For example, the formulation of a solid dosage form of an API may incorporate a release-modifying pharmaceutical carrier in order to achieve a desired release profile after

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administration of the compound. Polymer carriers such as a polyethylene oxide (PEO) polymer may be incorporated into a pharmaceutical composition to impart an extended release profile to the composition. PEO polymers are produced by a process of radical polymerization process followed by oxidative degradation of the polymer to achieve the desired molecular weight. The resulting PEO polymer carriers may retain residual peroxides and other oxidative species from the production process that may cause the oxidation of the API molecules in any pharmaceutical composition that incorporates PEO polymers. Typically, other excipients such as antioxidants or pH-lowering excipients may be incorporated into the API composition to minimize the degradation of the API in the presence of incompatible carriers such as PEO polymers in the pharmaceutical composition. However, in a solid dosage form composition, this approach is less effective than in other dosage forms such as solutions or suspensions.

Morphinans, a widespread class of analgesic APIs, are particularly vulnerable to oxidative degradation, especially in compositions that incorporate PEO polymer carriers or other pharmaceutical carriers that contain residual peroxides or other oxidative species. Because the physiological effects of morphinans are notoriously sensitive to small changes in chemical structure, the formation of degradants may introduce undesirable properties to a pharmaceutical composition in which a morphinan is vulnerable to degradation. For solid dosage forms of morphinan compositions, the introduction of additional antioxidant excipients or pH-lowering excipients to prevent the degradation of the morphinan, particularly when formulated in a solid dosage form, has been relatively ineffective to date.

A need exists in the art for a method of protecting an API from degradation in a solid dose form of a pharmaceutical composition. In particular, a need exists for a method of stabilizing morphinan APIs, which are especially vulnerable to oxidative degradation, in solid dosage forms of pharmaceutical compositions.

SUMMARY OF THE INVENTION

Briefly, therefore, one aspect of the disclosure provides a method for the preparation of a solid dosage form pharmaceutical composition comprising a morphinan and at least one other active pharmaceutical ingredient. The method comprises three steps. In the first step, a mixture comprising the morphinan and at least one excipient is granulated in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced thereby forming a morphinan-protected granule. The second step comprises granulating a mixture comprising the morphinan-protected granule, the active pharmaceutical agent, and at least one excipient to form a granulated mixture. In the third step, the granulated mixture is blended with a release-controlling polymer comprising a polyethylene oxide polymer to form the solid dosage form pharmaceutical composition comprising a sustained release layer.

In another aspect of the disclosure, a method for the preparation of a solid dosage form pharmaceutical composition comprising oxycodone and acetaminophen is provided. The method comprises three steps. In the first step, a mixture comprising the oxycodone and at least one excipient is granulated in a manner such that the amount of oxycodone exposed on the surface of the granule is substantially reduced thereby forming an oxycodone-protected granule. In the next step, a mixture comprising the oxycodone-protected granule, the acetaminophen, and at least one excipient is granulated to form a granulated mixture. The third step comprises blending

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the granulated mixture with a release-controlling polymer comprising a polyethylene oxide polymer is granulated to form the solid dosage form pharmaceutical composition comprising a sustained release layer.

An additional aspect of the disclosure provides a method for the preparation of a bilayer tablet comprising a sustained release layer and an immediate release layer. The method comprises four steps. In a first step, a mixture comprising oxycodone or hydrocodone and at least one excipient is granulated in a manner such that the amount of oxycodone or hydrocodone exposed on the surface of granule is substantially reduced thereby forming a morphinan-protected granule. In the next step, a mixture comprising the morphinan-protected granule, the acetaminophen, and at least one excipient is granulated to form a granulated mixture. In the third step, the granulated mixture is blended with a release-controlling polymer comprising a polyethylene oxide polymer to form a sustained release layer. In the final step, a mixture comprising the morphinan-protected granule from the first step is granulated with the acetaminophen and at least one excipient to form the immediate release layer.

A further aspect of the disclosure encompasses a granule that is substantially resistant to oxidative degradation of oxycodone. The granule comprises an interior region substantially comprising oxycodone that is surrounded by an exterior region substantially comprising at least one excipient. Moreover, the granule contains less than about 0.5% w/w of the total mass of oxycodone of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

Another aspect of the disclosure provides a granule substantially resistant to oxidative degradation of hydrocodone. The granule comprises an interior region substantially comprising hydrocodone that is surrounded by an exterior region substantially comprising at least one excipient, wherein the granule contains less than about 0.5% w/w of the total mass of hydrocodone of a degradant selected from hydrocodone-n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

Yet another aspect of the disclosure provides a granule substantially resistant to oxidative degradation of a morphinan, the granule prepared by a process comprising granulating a mixture comprising the morphinan and at least one excipient in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced thereby forming the morphinan-protected granule.

An additional aspect of the disclosure encompasses a pharmaceutical composition comprising a plurality of oxycodone-containing granules substantially resistant to oxidative degradation of oxycodone and at least one pharmaceutically acceptable carrier. The plurality of granules comprise an interior region substantially comprising oxycodone that is surrounded by an exterior region substantially comprising at least one excipient, wherein the granule contains less than about 0.5% w/w of the total mass of oxycodone of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

Another aspect of the disclosure provides a pharmaceutical composition comprising a plurality of hydrocodone-containing granules substantially resistant to oxidative degradation of hydrocodone and at least one pharmaceutically acceptable carrier. The plurality of granules comprise an interior region substantially comprising hydrocodone that is surrounded by an exterior region substantially comprising at least one excipient, wherein the granule contains less than about 0.5%

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w/w of the total mass of hydrocodone of a degradant selected from hydrocodone n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

Yet another aspect provides a solid dosage pharmaceutical composition comprising a plurality of oxycodone-protected granules and acetaminophen, the composition prepared by a process comprising (a) granulating a mixture comprising the oxycodone and at least one excipient in a manner such that the amount of oxycodone exposed on the surface of the granule is substantially reduced thereby forming the plurality of oxycodone-protected granules; (b) granulating a mixture comprising the plurality of oxycodone-protected granules, the acetaminophen, and at least one excipient to form a granulated mixture; and (c) blending the granulated mixture with a release-controlling polymer comprising a polyethylene oxide polymer to form the solid dosage form the pharmaceutical composition comprising a sustained release layer.

Other features and iterations of the invention are described in more detail below.

DETAILED DESCRIPTION

The invention provides methods of preparing morphinan-protected granules by combining a morphinan with at least one excipient to form a mixture, and granulating the mixture. The resulting morphinan-protected granules have a physical structure that minimizes the amount of morphinan that is exposed on the surface of the granule. The morphinan-protected granules may stabilize the morphinan against various mechanisms of degradation such as oxidation by substantially decreasing the amount of morphinan exposed on the surface of the granule thereby reducing the degree of contact between the morphinan and the oxidative species in the environment surrounding the granules, including but not limited to carriers and residual water in the composition, and atmospheric oxygen and moisture.

In addition, if chemically protective excipients including but not limited to antioxidants and pH-adjusting agents are included in the excipient mixture forming the morphinan-protected granule, the morphinan contained within the granule is further protected against degradation. Any oxidative species contained in the environment surrounding the morphinan-protected granules may react with the chemically protective excipients situated the granules before they can reach the morphinan.

The morphinan-protected granules may be prepared using any device known in the art, including but not limited to a high-shear wet granulator. The particular device used for granulation may affect the physical properties of the resulting granules, including but not limited to granule size, granule density, and granule porosity, all of which may influence the protective properties of the granule against degradation of the morphinan. Regardless of the granulation method used to form the granules, the distribution of morphinan and excipients within the granules is influenced by at least several factors including but not limited to the size of the morphinan particles relative to the excipient particles in the mixture prior to granulation, the chemical properties of the morphinan and excipients including but not limited to hydrophobicity and ionic charge, and the presence of excipients dissolved in the granulation solution used to prepare the granules.

The morphinan-protected granules prepared by the methods of the invention may be incorporated into a solid dose form of a pharmaceutical composition, including but not limited to tablet and capsule formulations. In addition to protection against degradation, the inclusion of the morphinan in the

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form of granules imparts several other advantageous aspects to the resulting composition. Because the morphinan in the granules is protected, the choice of carrier may be selected to satisfy constraints other than compatibility with the morphinan. Carriers in the composition may instead be selected based on factors including but not limited to the cost of the carrier, the desirable modified-release properties imparted by a particular carrier. Further, variation in the characteristics of the morphinan-protected granules including granule size, excipients included in the granules, and the physical structure of the granules may be used to control the release profile or other pharmacokinetic characteristics of pharmaceutical compositions.

Detailed descriptions of various embodiments of the morphinan protected granules, methods of preparing the morphinan protected granules, and solid dosage forms of pharmaceutical compositions that include the morphinan-protected granules are described in detail below.

(I) Morphinan-Protected Granules

The granules prepared by the methods of the invention stabilize the morphinan contained within the granules by substantially reducing the amount of morphinan exposed on the surface of the granule. In this regard, significantly less of the morphinan is in contact with any oxidative species in the environment outside of the granule, and may additionally provide chemical protection of the morphinan against degradation by surrounding the morphinan with chemically protective excipients including but not limited to antioxidants that are contained within the morphinan-protected granule. The physical structure of the morphinan-protected granule may influence the protective efficacy of the granule against degradation of the morphinan, and further influences the suitability of the granules for inclusion in various solid dose forms of pharmaceutical compositions, including but not limited to tablets and capsules.

(a) Granule Structure

The physical structure of the granule includes the morphinan dispersed within the excipient mixture and granulated in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced. The particular physical structure of any embodiment of a morphinan-protected granule is influenced by at least several factors related to the method of preparing the granules and the particular morphinan and excipients included in the granule. The influence of these factors on the physical structure of the granules is described in detail below.

In general, the physical structure of the granules may vary from an essentially random spatial distribution of the morphinan and excipients throughout the granules to a highly ordered distribution in which essentially all of the morphinan is contained within a sharply delineated interior region that is surrounded by an exterior region that contains essentially all of the excipients. In an embodiment, the amount of morphinan that is exposed at the surface of the granules is less than about 100% of the total weight of the morphinan in the granules. In other embodiments, the amount of morphinan that is exposed at the surface of the granules is less than about 95%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, and less than about 5% of the total weight of morphinan in the granule.

Excipients contained within the granule may provide additional protection against degradation of the morphinan by chemically interacting with degradative compounds surrounding or within the granule. For example, the effectiveness of the excipients at protecting the morphinans in the

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granule may be enhanced if at least one of the excipients includes but is not limited to an antioxidant, a chelating agent, or a pH-adjusting agent. Various embodiments of the excipients included in the granule are described in detail below.

The density and porosity of the exterior regions of the granules may influence the effectiveness of the exterior regions at protecting the morphinans in the granules from degradation. Exterior regions having higher densities and lower porosities may be more resistant to penetration by degradative compounds from outside the granule. The densities and porosities of the exterior regions of the granules may be influenced by at least several factors including but not limited to the particular morphinan and excipients included in the granule and the device used to prepare the granule. For example, a granule prepared using a high-shear wet granulator may have a higher density and lower porosity compared to a granule with a similar composition prepared using a fluid bed granulator.

The d_{90} of the granules in various embodiments may be selected based on the intended use of the granules, in particular the particular solid dosage form in which the granules are to be incorporated. The particular d_{90} of the granule may be influenced by a variety of factors including but not limited to the composition of the granule and the granulation device used to prepare the granules. The d_{90} of the granules may be larger for granule compositions having a higher proportion of excipients including but not limited to binders and fillers relative to other types of excipients.

In various embodiments, the granules may have an average d_{90} of less than about 2000 μm . In other embodiments, the granules may have an average d_{90} of less than about 1800 μm , less than about 1500 μm , less than about 1000 μm , less than about 900 μm , less than about 800 μm , less than about 700 μm , less than about 600 μm , less than about 500 μm , less than about 400 μm , less than about 300 μm , less than about 200 μm , less than about 150 μm , and less than about 100 μm . In one exemplary embodiment in which the granules are to be incorporated in a solid dosage form including but not limited to a capsule, the granules may be less than about 1000 μm in average d_{90} . In another exemplary embodiment in which the granules are to be incorporated in a solid dosage form including but not limited to a tablet, the granules may be less than about 800 μm in average d_{90} . In yet another embodiment, the granules may range from about 150 μm to about 200 μm in average d_{90} .

(II) Granule Composition

The composition of the granules prepared using the methods of the invention include a morphinan and at least one excipient. The particular composition of the granules may influence a variety of properties of the granules including but not limited to the physical structure of the granules, the stability of the morphinan contained within the granule, and the suitability of the granules for incorporation into a particular dry dosage form of a pharmaceutical composition.

One aspect of the composition that may influence the physical structure of the granules is the d_{90} of the morphinan particles relative to the d_{90} of the excipient particles in the mixture that used to form the granules. As used herein, d_{90} represents the particle diameter at which 90% of the individual particles of a compound are smaller than the specified diameter. Without being bound to any particular theory, when a granulation device including but not limited to a low-shear wet granulator, a high-shear wet granulator, or a fluid bed granulator is used to granulate the mixture of the morphinan and at least one excipient, the compounds having a smaller d_{90} relative to the other compounds in the mixture tend to aggregate near the interior regions of the granules, and the compounds having larger d_{90} tend to aggregate near the exte-

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rior regions of the granules, regardless of whether the compound is a morphinan or an excipient.

As a practitioner skilled in the art may appreciate, for granule compositions in which the morphinan accounts for an extremely low proportion of the total mass of the granule, the size of the morphinan particles relative to the excipient particles may not exert the same influence on the physical structure of the resulting granules as described previously. By way of a non-limiting example, if a granule is prepared using a mixture containing about 5% morphinan and about 95% excipients by weight, and the d_{90} of the morphinan is larger than the d_{90} of the excipients, the relative scarcity of the morphinan particles may result in a granule in which the individual morphinan particles are surrounded by excipient particles, and the morphinan particles may be located in both the interior region and the exterior region of the granule.

In one embodiment, the d_{90} of the morphinan is smaller than the d_{90} of the excipients. In another embodiment, the d_{90} of the morphinan is less than about 80% of the d_{90} of the excipients. In yet other embodiments, the d_{90} of the morphinan is less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, or less than about 50% of the d_{90} of the excipients.

The d_{90} values of the morphinan and the excipients may also be influenced by the capabilities of the particular device used to prepare the granules. Without being bound to any particular theory, when a granulation device including but not limited to a low-shear wet granulator, a high-shear wet granulator, or a fluid bed granulator is used to granulate the mixture of the morphinan and at least one excipient, if the d_{90} of a particular compound falls below a threshold d_{90} , the particles of that compound tend to aggregate before they are granulated, resulting in granules that have a non-homogenous distribution of the compound from granule to granule.

In other embodiments, other properties of the morphinan and excipients may influence the physical structure of the granule including but not limited to the hydrophobicity and ionic charge of the morphinan relative to the one or more excipients. As a non-limiting illustrative example, if the morphinan is hydrophobic relative to the excipients and if a polar granulation fluid is used in the granulation process, hydrophobic repulsive forces may tend to situate the morphinan within the interior region of the granules.

In one embodiment, the composition of the granules includes one morphinan compound. In other embodiments, the composition of the granules may further include one or more additional morphinan compounds within each granule. Any number of different morphinans may be included in the composition of the granules, so long as all morphinans that are included in the granule are physically and chemically compatible.

An acid, as defined herein, refers to the acid and any pharmaceutically acceptable salt of the acid.

(a) Morphinans

The compositions of various embodiments of the granules include a morphinan. In one embodiment, the morphinan may be included in the granules in an amount of up to about 90% of the total weight of the granules. In other embodiments, the morphinan may be included in the granules in an amount ranging up to about 80%, up to about 70%, up to about 60%, up to about 50%, up to about 40%, up to about 30%, up to about 20%, up to about 10%, up to about 1%, and up to about 0.5% of the total weight of the granules.

The morphinan included in various embodiments of the granules may be selected from opium, natural opium derivatives, semi-synthetic opium derivatives, and synthetic opium derivatives. Non-limiting examples of suitable morphinans for various embodiments of the granules include adlumine, allocryptopine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bulbocapnine, buprenorphine, butorphanol,

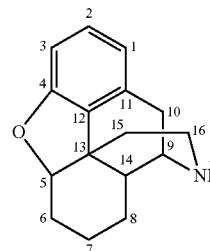
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canadine, capaurine, chelerythrine, chelidone, codamine, codeine, coptisine, coreximine, corlumine, corybulbine, corycavamine, corycavine, corydaline, corydine, corytuberine, cularine, cotamine, cryptopine, cycloartenol, cycloartenone, cyclolaudenol, dehydrotectine, desomorphine, dextropropoxyphene, dextrophanol, diacetylmorphine, dicentrine, dihydrosanguinarine, dipropanoylmorphine, epiporphyroxine, ethylmorphine, eupaverine, fagarine, fentanyl, glaucine, homochelidonine, hydrocodone, hydrocotamine, hydromorphone, hydroxythebaine, isoboldine, isocorybulbine, isocorydine, isocorypalmine, isoquinoline, laudanidine, laudanine, laudanone, levorphanol, magnoflorine, meconic acid, methadone, morphine, nalbuphine, nalmefene, naloxone, naltrexamine, α -naltrexol, β -naltrexol, naltrexone, naphthaphenanthridine, narceine, narceinone, narcotoline, narcotine, neopine, nicomorphine, norlaudanoline, norsanguinarine, noscapine, opium, oripavine, oxycodone, oxymorphone, oxysanguinarine, palaudine, papaverine, papaveraldine, papaverrubine, perparin, pethidine, phenanthrene, phtalide-isoquinoline, porphyroxine, protopine, pseudocodeine, pseudomorphine, reticuline, salutaridine, sinoacutine, sanguinarine, scoulerine, somniferine, stepholidine, tapentadol, tetrahydroprotoberberine, thebaine, tramadol, and xanthaline. In an exemplary embodiment, the morphinan included in the granules may be selected from oxycodone, oxymorphone, hydrocodone, hydromorphone, nalbuphine, naloxone, buprenorphine, and naltrexone. In another exemplary embodiment, the morphinan in the granules is oxycodone or hydrocodone.

Any of the morphinans included in the embodiments of the granules may have a (-) or (+) orientation with respect to the rotation of polarized light, depending upon whether the starting substrate has (-) or (+) optical activity, and are referred to herein as (-)-morphinans and (+)-morphinans respectively. More specifically, each chiral center may independently have an R or an S configuration.

As an illustrative example, an embodiment of the granules may include a morphinan compound possessing a fused carbon ring structure. The ring atoms of the morphinan compound may be numbered as diagrammed in Formula (I) below. Morphinan compounds have asymmetric centers and the core morphinan compound may have at least four chiral carbons including but not limited to C-5, C-13, C-14, and C-9. In various embodiments, the configuration of the chiral carbons C-5, C-13, C-14, and C-9 may be RRRR, RRSR, RRRS, RRSS, RSRR, RSSR, RSRS, RSSS, SRRR, SRSR, SRSS, SSRR, SSSR, SSRS, or SSSS, provided that the C-15 and the C-16 carbons are both oriented either on the alpha face or the beta face of the morphinan molecule.

(I)



In various embodiments of the granules, the morphinan may be provided in any solid form including but not limited to a finely divided solid, a crystal, a particle, a powder, or any other finely divided solid form known in the art. Any finely divided solid form of the morphinan may be used so long as

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the d_{90} of the morphinan particles are smaller than the d_{90} of the one or more excipients as described above.

(b) Excipients

Various embodiments of the granules include one or more excipients in addition to the morphinan. In general, the one or more excipients are selected to impart at least one or more desired physical or chemical properties to the granules, including but not limited to adhesion of the particles of the morphinan and excipient compounds in the mixture to facilitate the formation of granules, formation of physical barriers around the morphinans in the granules, and chemical inhibition of various mechanisms of degradation of the morphinans including but not limited to oxidation. Non-limiting examples of the one or more excipients include binders, fillers, antioxidants, pH-adjusting agents, chelating agents, and antimicrobial agents.

In one embodiment, the one or more excipients may be introduced into the mixture to be granulated in a solid form including but not limited to a crystal, a particle, a powder, or any other finely divided solid form known in the art. In another embodiment, the one or more excipients may be dissolved or suspended in a solvent and sprayed onto the mixture in a granulation device as a binder fluid during granulation.

(i) Binders

In general, binders are excipients included in various embodiments of the granule to impart structural integrity to the granules by binding together the particles making up each granule. Non-limiting examples of binders suitable for the formulations of various embodiments include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof. The polypeptides may be any arrangement of amino acids ranging from about 100 to about 300,000 Daltons.

In one embodiment, the binder may be introduced into the mixture to be granulated in a solid form including but not limited to a crystal, a particle, a powder, or any other finely divided solid form known in the art. In another embodiment, the binder may be dissolved or suspended in a solvent and sprayed onto the mixture in a granulation device as a binder fluid during granulation.

(ii) Fillers

Fillers may be included in various embodiments of the granule composition as an excipient to increase the bulk volume of the granules and to impart suitable compressibility characteristics to the granules for subsequent inclusion in solid dosage forms of pharmaceutical compositions including but not limited to tablets. Non-limiting examples of fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. Other non-limiting examples of fillers include dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol.

(iii) Antioxidants

Antioxidants are excipients included in various embodiments of the granules to prevent the oxidation of the morphinan in the granules. Suitable antioxidants include, but are not limited to anoxomer, N-acetylcysteine, benzyl isothiocyanate, m-aminobenzoic acid, o-aminobenzoic acid, p-aminobenzoic acid (PABA), butylated hydroxyanisole (BHA),

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butylated hydroxytoluene (BHT), caffeic acid, canthaxanthin, alpha-carotene, beta-carotene, beta-carotene, beta-apocarotenoid acid, camosol, carvacrol, catechins, chlorogenic acid, citric acid and its salts, clove extract, coffee bean extract, p-coumaric acid, 3,4-dihydroxybenzoic acid, N,N'-diphenyl-p-phenylenediamine (DPPD), dilauryl thiodipropionate, distearyl thiodipropionate, 2,6-di-tert-butylphenol, edetic acid, ellagic acid, erythorbic acid, sodium erythorbate, esculetin, esculin, 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline, ethyl maltol, ethylenediaminetetraacetic acid (EDTA) and EDTA salts, eucalyptus extract, eugenol, ferulic acid, flavonoids (e.g., catechin, epicatechin, epigallocatechin (EGC), flavones (e.g., apigenin, chrysin, luteolin), flavonols (e.g., datiscetin, myricetin, daemfero), flavanones, fraxetin, fumaric acid, gallic acid, gentian extract, gluconic acid, glycine, gum guaiacum, hesperetin, alpha-hydroxybenzyl phosphonic acid, hydroxycinnamic acid, hydroxyglutaric acid, hydroquinone, N-hydroxysuccinic acid, hydroxytyrosol, hydroxyurea, rice bran extract, lactic acid and its salts, lecithin, lecithin citrate; R-alpha-lipoic acid, lutein, lycopene, malic acid, maltol, 5-methoxy tryptamine, monoglyceride citrate; monoisopropyl citrate; morin, beta-naphthoflavone, nordihydroguaiaretic acid (NDGA), oxalic acid, palmitic citrate, phenothiazine, phosphatidylcholine, phosphoric acid, phosphates, phytic acid, phytolubichromel, pimento extract, polyphosphates, quercetin, trans-resveratrol, rosemary extract, rosmarinic acid, sage extract, sesamol, silymarin, sinapic acid, succinic acid, stearyl citrate, syringic acid, tartaric acid, thymol, tocopherols (i.e., alpha-, beta-, gamma- and delta-tocopherol), tocotrienols (i.e., alpha-, beta-, gamma- and delta-tocotrienols), tyrosol, vanilic acid, 2,6-di-tert-butyl-4-hydroxymethylphenol (i.e., lonox 100), 2,4-(tris-3',5'-bi-tert-butyl-4'-hydroxybenzyl)-mesitylene (i.e., lonox 330), 2,4,5-trihydroxybutyrophenone, ubiquinone, tertiary butyl hydroquinone (TBHQ), thiodipropionic acid, trihydroxy butyrophenone, tryptamine, tyramine, uric acid, vitamin K and derivatives, vitamin Q10, wheat germ oil, zeaxanthin, or combinations thereof.

In another embodiment, an antioxidant agent may be subjected to a particle size reduction process including but not limited to grinding, milling, sonication, or hammer milling in order to reduce the d_{90} of the antioxidant agent to a value less than the d_{90} of the morphinan (or other API included in the formulation) prior to granulation. In this embodiment, the reduced d_{90} of the antioxidant agent may result in a distribution of antioxidant agent that is clustered around the morphinan particles, rather than near the outer surface of the granule. A granule having this physical structure may provide comparable protection of the morphinan in the granules against degradation as compared to granules in which the antioxidant agent is situated on the outside of the granule using a significantly lower amount of the antioxidant agent.

In an exemplary embodiment, the granule composition includes at least one antioxidant including but not limited to citric acid and Na_2EDTA .

(iv) pH-Adjusting Agents

In various embodiments of the granule composition, a pH-adjusting agent may be included as an excipient to raise or lower the pH of the granule in order to prevent the oxidation of the morphinan in the granules. For example, a pH-adjusting agent including but not limited to citric acid may be incorporated into the composition granule in order to lower the pH of the granule. In this example, a lower pH prevents the oxidation of the granule by various oxidative compounds associated with release-modifying polymer incorporated into a solid dosage form, including but not limited to peroxides.

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In another embodiment, a pH-adjusting agent may be subjected to a particle size reduction process including but not limited to grinding, milling, sonication, or hammer milling in order to reduce the d_{90} of the pH-adjusting agent to a value less than the d_{90} of the morphinan prior to granulation. In this embodiment, the reduced d_{90} of the pH-adjusting agent may result in a distribution of pH-adjusting agent that is clustered around the morphinan particles, rather than near the outer surface of the granule. Non-limiting examples of pH-adjusting agents include citric acid, acetic acid, tartaric acid, malic acid, fumaric acid, lactic acid, phosphoric acid, sorbic acid, benzoic acid, sodium carbonate and sodium bicarbonate.

(v) Chelating Agents

In various embodiments of the granule composition, a chelating agent may be included as an excipient to immobilize oxidative species including but not limited to metal ions in order to inhibit the oxidative degradation of the morphinan by these oxidative species. Non-limiting examples of chelating agents include lysine, methionine, glycine, gluconate, polysaccharides, glutamate, aspartate, and Na_2EDTA .

(vi) Antimicrobial Agents

In various embodiments of the granule composition, an antimicrobial agent may be included as an excipient to minimize the degradation of the morphinan by microbial agents including but not limited to bacteria and fungi. Non-limiting examples of antimicrobials include parabens, chlorobutanol, phenol, calcium propionate, sodium nitrate, sodium nitrite, Na_2EDTA and sulfites including but not limited to sulfur dioxide, sodium bisulfite, and potassium hydrogen sulfite.

(III) Granule Stability

In various embodiments of the granule composition, the morphinan in the granule is substantially resistant to degradation due to interactions of the morphinan with degradative compounds or conditions present in the environment or in the carriers surrounding the granules in a solid dosage form of a pharmaceutical composition. In one embodiment, the morphinan in the granules is substantially resistant to the formation of degradants resulting from a chemical change in the morphinan brought about during the production and/or storage of the pharmaceutical composition containing the morphinan by the effect of factors including but not limited to light, temperature, pH, water, or reaction with an excipient or carrier included in the pharmaceutical composition. The particular degradants formed in a pharmaceutical composition depend on the particular morphinan and the at least one excipient within the granule, as well as the particular carriers included in the pharmaceutical composition along with the granules.

Statutory requirements, including but not limited to ICH Guidelines Q3A and Q3B identify maximum allowable amounts of degradants above which the degradants must be reported and subjected to the qualification process described above. According to ICH Guideline Q3B, the amount of any individual degradant must be reported if the amount of degradant exceeds 0.10% of the total API weight for maximum daily doses of 1000 mg of API or below. For APIs having average daily doses of above 1000 mg, degradants in excess of 0.05% of the total API mass must be reported. The ICH guidelines apply throughout the effective shelf life of the pharmaceutical composition.

Although no standardized method of assessing API stability exists at present, drug developers typically subject potential pharmaceutical compounds to periods of storage at accelerated degradation conditions, typically defined as a temperature of about 40° C. and a relative humidity of about

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75%. The period of storage time at the accelerated degradation conditions may vary from about 1 day to about 6 months, but is typically about 6 months. In an embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than 0.05%, less than 0.04%, less than 0.03%, less than 0.02%, or less than 0.01% of the total mass of the morphinan after about two months of storage at a temperature of about 40° C. and a relative humidity of about 75%. In another embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than 0.05%, less than 0.04%, less than 0.03%, less than 0.02%, or less than 0.01% of the total mass of the morphinan after about six months of storage at a temperature of about 40° C. and a relative humidity of about 75%. In yet another embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than 0.05%, less than 0.04%, less than 0.03%, less than 0.02%, or less than 0.01% of the total mass of the morphinan after about four weeks of storage at accelerated stability conditions at a temperature of about 40° C. and a relative humidity of about 75%.

In an exemplary embodiment, for a pharmaceutical composition incorporating oxycodone as the morphinan and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of oxycodone of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity. In another exemplary embodiment, for a pharmaceutical composition incorporating oxycodone and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of oxycodone of each of one or more degradants selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

In another exemplary embodiment, for a pharmaceutical composition incorporating hydrocodone as the morphinan and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of hydrocodone of a degradant selected from hydrocodone n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity. In another exemplary embodiment, for a pharmaceutical composition incorporating hydrocodone and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of hydrocodone of each of one or more degradants selected from hydrocodone n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

(IV) Method of Preparing Granules

In various embodiments, the granules may be prepared by combining the morphinan with at least one excipient to form a mixture and granulating the mixture in a manner such that the amount of morphinan exposed on the surface of the granules is minimized (thereby forming a morphinan-protected granule).

Suitable morphinans for the granule embodiments are described in detail in Section (IIa) above, and suitable excipients are described in Section (IIb) above. The mixture may be formed using any suitable method known in the art including but not limited to stirring, shaking, vibrating, and blending. In

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an embodiment, the morphinan and dry excipients may be charged into a granulation device and mixed prior to the addition of the granulation fluid.

Any suitable granulation device known in the art may be used to prepare the granules. As previously discussed, the particular granulation device selected for the preparation of the granules may influence the physical properties of the resulting granules. Non-limiting examples of suitable devices for the preparation of the granules include a low-shear wet granulator, a high-shear wet granulator, a fluid-bed granulator, a roller compactor, a vertical granulator, an oscillating granulator, a gelatinizer, a pelletizer, and a spheronizer. The granulation device may be selected in order to prepare granules having the desired granule physical characteristics described in Section (II) above.

In an exemplary embodiment, a high-shear wet granulator is used to prepare the granules. The high-shear wet granulator may be capable of preparing granules having properties that enhance the protective effect of the granule, including but not limited to higher granule densities and lower granule porosities relative to granules prepared by other devices. Further, the high-shear wet granulator is capable of preparing granules with a d_{50} that is larger than other granulation devices, resulting in granules suitable for inclusion in a wider variety of solid dosage forms of morphinan compositions.

In the same exemplary embodiment, the morphinan and the excipients in dry form of the composition are introduced into the wet high shear granulator in order to form the mixture. After the morphinan and the dry excipients are essentially homogeneously distributed within the granulator, a granulation fluid is sprayed into the granulator. In various embodiments, the granulation fluid may be any volatile, non-toxic granulation fluid known in the art. Non-limiting examples of suitable granulation fluids include water, ethanol, isopropanol, and combinations thereof. In other embodiments, one or more of the excipients may be mixed with the granulation fluid prior to spraying the granulation fluid into the granulator. In an exemplary embodiment, a binder including but not limited to pregelatinized starch may be dissolved into the granulation fluid including but not limited to water to form a granulation solution, and the granulation solution may be sprayed into the granulator in order to prepare the granules.

In an additional embodiment, the wet granules prepared in the high shear wet granulator may be dried using a drying device, resulting in dried granules having a water content of less than about 5%, less than about 4%, less than about 3%, or less than about 2% of the total weight of the granules. Any suitable drying device known in the art may be used to dry the wet granules, including but not limited to an oven, a vacuum oven, and a rotary drum dryer.

(V) Solid Dosage Forms Incorporating Granules

The morphinan-protected granules prepared by various embodiments may be incorporated into various solid dosage pharmaceutical compositions. Non-limiting examples of solid dosage pharmaceutical compositions incorporating embodiments of the morphinan granules include granules, tablets, and capsules. Non-limiting embodiments of tablets include uncoated tablets, coated tablets, mini-tablets, orally disintegrating tablets, and bilayer tablets. Non-limiting embodiments of capsules include hard capsules and multi-layer capsules. Depending on the selection of particular formulation, the solid dosage pharmaceutical composition may have release characteristics including but not limited to rapid release, sustained release, extended release, slow release, time release, and combinations thereof.

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In an exemplary embodiment, solid dosage form pharmaceutical compositions are made via a two step process. First, the morphinan-protected granule is formed. The morphinan-protected granule is then mixed with excipients and other active pharmaceutical ingredients, which are then granulated to form the solid dosage form pharmaceutical composition. The solid dosage form pharmaceutical composition may include additional APIs. In an exemplary embodiment, the solid dosage form pharmaceutical composition comprises a morphinan and acetaminophen. In additional embodiments, the solid dosage form pharmaceutical composition may comprise sustained release (SR) and immediate release layers (IR). Typically, the SR and IR layers both include the morphinan and acetaminophen. In each of the foregoing embodiments, the SR layer typically comprises a release-controlling polymer comprising a polyethylene oxide polymer.

(a) Compositions of Solid Dosage Forms

Various embodiments of the solid dosage pharmaceutical compositions incorporating the morphinan-protected granules may include one or more pharmaceutically acceptable carriers in addition to the granules. Pharmaceutically acceptable carriers suitable for embodiments of the solid dosage pharmaceutical compositions may include but are not limited to binders, fillers, lubricants, diluents, non-effervescent disintegrants, effervescent disintegrants, flavor-modifying agents, sweeteners, dispersants, coloring agents, taste masking agents, release-controlling polymers and combinations thereof.

(i) Binders

Non-limiting examples of binders suitable for the formulations of various embodiments include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof. The polypeptide may be any arrangement of amino acids ranging from about 100 to about 300,000 Daltons.

(ii) Fillers

Non-limiting examples of fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. Other non-limiting examples of fillers include dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol.

(iii) Lubricants

Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and light mineral oil.

(iv) Diluents

Diluents suitable for use include but are not limited to pharmaceutically acceptable saccharides such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, and sorbitol; polyhydric alcohols; starches; pre-manufactured direct compression diluents; and mixtures of any of the foregoing.

(v) Non-Effervescent and Effervescent Disintegrants

Non-limiting examples of non-effervescent disintegrants include starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, sodium

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starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, and tragacanth. Suitable effervescent disintegrants include but are not limited to sodium bicarbonate in combination with citric acid, and sodium bicarbonate in combination with tartaric acid.

(vi) Flavor-Modifying Agents

Suitable flavor-modifying agents include but are not limited to synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits, and combinations thereof. Other non-limiting examples of flavor-modifying agents include cinnamon oils, oil of wintergreen, peppermint oils, clover oil, hay oil, anise oil, eucalyptus, vanilla, citrus oils such as lemon oil, orange oil, grape and grapefruit oil, fruit essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, and apricot.

(vii) Sweeteners

Non-limiting examples of sweeteners include glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; *Stevia rebaudiana* (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof.

(viii) Dispersants

Dispersants may include but are not limited to starch, alginate, polyvinylpyrrolidones, guar gum, kaolin, bentonite, purified wood cellulose, sodium starch glycolate, isoamorphous silicate, and microcrystalline cellulose as high HLB emulsifier surfactants.

(ix) Coloring Agents

Suitable coloring agents include but are not limited to food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors or dyes, along with their corresponding lakes, and certain natural and derived colorants may be suitable for use in various embodiments.

(x) Taste-Masking Agents

Taste-masking agents include but are not limited to cellulose hydroxypropyl ethers (HPC) such as Klucel®, Nisswo HPC and PrimaFlo HP22; low-substituted hydroxypropyl ethers (L-HPC); cellulose hydroxypropyl methyl ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Opadry YS, PrimaFlo, MP3295A, Benecel MP824, and Benecel MP843; methylcellulose polymers such as Methocel® and Metolose®; Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease; Polyvinyl alcohol (PVA) such as Opadry AMB; hydroxyethylcelluloses such as Natrosol®; carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualone®-CMC; polyvinyl alcohol and polyethylene glycol copolymers such as Kollicoat IR®; monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® RD100, and Eudragit® E100; cellulose acetate phthalate; sepiifilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials. In other embodiments, additional taste-masking agents contemplated are those described in U.S. Pat. Nos. 4,851,226, 5,075,114, and 5,876,759, each of which is hereby incorporated by reference in its entirety.

(xi) Release-Controlling Polymers

Release-controlling polymers may be included in the various embodiments of the solid dosage pharmaceutical compo-

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sitions incorporating the granules. In one embodiment, the release-controlling polymers may be used as a tablet coating. In other embodiments, including but not limited to bilayer tablets, a release-controlling polymer may be mixed with the granules and other excipients prior to the formation of a tablet by a known process including but not limited to compression in a tablet mold. Suitable release-controlling polymers include but are not limited to hydrophilic polymers and hydrophobic polymers.

Suitable hydrophilic polymers include, but are not limited to, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose ethers, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, nitrocellulose, crosslinked starch, agar, casein, chitin, collagen, gelatin, maltose, mannitol, maltodextrin, pectin, pullulan, sorbitol, xylitol, polysaccharides, ammonia alginate, sodium alginate, calcium alginate, potassium alginate, propylene glycol alginate, alginate sodium carmellose, calcium carmellose, carrageenan, fucoidan, furcellaran, arabic gum, carrageens gum, ghatti gum, guar gum, karayagum, locust bean gum, okragum, tragacanth gum, scleroglucan gum, xanthan gum, hypnea, laminaran, acrylic polymers, acrylate polymers, carboxyvinyl polymers, copolymers of maleic anhydride and styrene, copolymers of maleic anhydride and ethylene, copolymers of maleic anhydride propylene or copolymers of maleic anhydride isobutylene), crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, diesters of polyglucan, polyacrylamides, polyacrylic acid, polyamides, polyethylene glycols, polyethylene oxides, poly(hydroxyalkyl methacrylate), polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, polystyrenes, polyvinylpyrrolidone, anionic and cationic hydrogels, and combinations thereof.

Non-limiting examples of suitable hydrophobic polymers include cellulose acetate butyrate, cellulose acetate ethylcarbamate, cellulose acetate heptanoate, cellulose acetate methylcarbamate, cellulose acetate octanoate, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate succinate, cellulose acetate trimaletate, cellulose acetaldehyde dimethyl acetate, cellulose butyrate, cellulose dimethylaminoacetate, cellulose disuccinate, cellulose dipalmitate, cellulose dicaprylate, cellulose propionate, cellulose propionate succinate, cellulose trioctanoate, cellulose tripropionate, cellulose trimellitate, cellulose tripalmitate, cellulose trivalerate, cellulose valerate palmitate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, ethylhydroxy ethylcellulose, hydroxy propyl methylcellulose phthalate, methyl cellulose, methyl ethyl cellulose, propyl cellulose, sodium carboxymethyl starch, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, methacrylic acid copolymers, methacrylic acid ester copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylate), poly(methacrylate), poly(methyl methacrylate), poly(ethylacrylate), poly(ethyl methacrylate), poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, ammonio methacrylate copolymers, lecithins, aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, hydrogenated vegetable oil, 12-hydroxystearyl alcohol, glyceryl monopalmitate, glyceryl dipalmitate, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, myristyl alcohol, stearic acid, stearyl alcohol, polyethyleneglycols, zein, shellac, bee's wax, carnauba wax, glyceryl behenate, Japan wax, paraffin, spermaceti, synthetic waxes, and combinations thereof.

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(b) Methods of Producing Solid Dosage Forms

The solid dosage pharmaceutical compositions may be produced using any suitable method known in the art. The particular production method selected may depend on the desired type of solid dosage form and the desired release profile.

(i) Production of Tablet Compositions

The pharmaceutical compositions in the form of a tablet may be produced using any suitable method known in the art including but not limited to direct compression, wet granulation, dry granulation, and combinations thereof. In one embodiment, the morphinan-protected granules may be combined with the one or more carriers and granulated into tablet granules using any of the known granulation devices described previously. In this same embodiment, the tablet granules formed from the combination of the morphinan-protected granules and the one or more carriers may be optionally blended with one or more additional carriers including but not limited to lubricants, and the resulting tablet blend may be compressed into a tablet form. In another embodiment, one or more carriers incorporated into the tablet granules may include a release-controlling polymer to impart a modified release profile to the resulting tablet.

In yet another embodiment, a bilayer tablet may be formed by producing a first tablet blend and a second tablet blend using a tablet granulation and blending process similar to those previously described. In this embodiment, the first tablet blend may include a disintegrant in order to impart a rapid release profile to the resulting tablet produced using the first tablet blend. The second tablet blend of this embodiment may include a release-controlling polymer to impart a modified release profile to the resulting tablet produced using the second tablet blend. The first tablet blend and the second tablet blend may be loaded into a tableting device including but not limited to a bilayer tablet press, and pressed into a bilayer tablet in which the first layer may have a rapid release profile and the second layer may have a modified release profile.

In yet another embodiment, the morphinan-protected granules may be coated with a release-controlling polymer prior to incorporating the morphinan-protected granules into a solid tablet form in order to impart a modified release profile to the resulting tablet. In an additional embodiment, the solid tablet form may be coated with a release-controlling polymer to impart a modified release profile. Other combinations of the embodiments described above may be used to produce additional embodiments having a desired release profile or other desired performance characteristic including but not limited to masked taste, acceptable tongue-feel and mouth-feel, and enhanced stability.

(ii) Production of Capsule Compositions

The pharmaceutical compositions in the form of a capsule may be produced using any suitable method known in the art including but not limited to direct loading into two-piece telescoping hard capsules. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, and hard cellulose capsules. In one embodiment, the capsule form of the pharmaceutical compositions may be produced by loading the morphinan-protected granules in to the hard capsule and sealing the capsule. In other embodiments, the morphinan-protected granules may be coated with a release-controlling polymer to impart a modified release profile to the hard capsule composition. In yet other embodiments, a fraction of the morphinan-protected granules may be coated with a release-controlling polymer and combined with

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the remaining uncoated morphinan-protected granules prior to loading the granules into the hard capsule.

(VI) Exemplary Embodiments

Exemplary embodiments of a granule and a solid dose pharmaceutical composition are described below.

(a) Oxycodone-Protected Granule

An exemplary embodiment of a granule includes oxycodone, microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid. The overall composition of the exemplary oxycodone-protected granule embodiment is listed in Table 10 below. In this embodiment, the granules may be formed using the wet granulation method described in Example 5 below. In this embodiment, the oxycodone granules have a granule d₉₀ ranging from about 100 μm to about 400 μm, and contain less than about 2% water by weight.

(b) Bilayer Oxycodone/APAP Tablet

An exemplary embodiment of a solid dose pharmaceutical composition may be a bilayer tablet that includes the oxycodone-protected granules described above. The exemplary bilayer tablet may be formed using the method described in Example 2 below. The two layers of the bilayer tablet in this embodiment include an immediate release (IR) layer and a sustained release (SR) layer. The overall compositions of the IR layer and the sustained release layer of the exemplary bilayer tablet embodiment are listed in Table 1 below. The stability of the oxycodone in the exemplary bilayer tablet composition that incorporates oxycodone in a granular form is significantly better than a similar bilayer tablet composition that incorporates oxycodone in an unprotected powder form, as described in Example 2 below.

TABLE 1

Composition of Exemplary Oxycodone Bilayer Tablet Composition

Compound	Dry Wt. (% total)	
	IR Layer	SR Layer
Protected oxycodone granules	2.99%	2.62%
APAP	77.73%	22.73%
MCC	4.82%	26.81%
Hydroxypropyl cellulose	7.71%	1.34%
Cross carmellose sodium	6.00%	
Silicon dioxide	0.50%	0.5%
Magnesium stearate	0.25%	1.0%
Polyethylene oxide polymer		45.0%

(c) Hydrocodone-Protected Granule

An exemplary embodiment of a granule includes hydrocodone, microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid. The overall composition of the exemplary hydrocodone-protected granule embodiment is listed in Table 13 below. In this embodiment, the granules may be formed using the wet granulation method described in Example 6 below. In this embodiment, the hydrocodone granules have a granule d₉₀ ranging from about 100 μm to about 400 μm after milling, and contain less than about 5% water by weight.

(d) Bilayer Hydrocodone/APAP Tablet

An exemplary embodiment of a solid dose pharmaceutical composition may be a bilayer tablet that includes the hydrocodone-protected granules described above. The exemplary bilayer tablet may be formed using the method described in Example 2 below. The two layers of the bilayer tablet in this embodiment include an immediate release (IR) layer and a sustained release (SR) layer. The overall compositions of the

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IR layer and the sustained release layer of the exemplary bilayer tablet embodiment are listed in Table 2 below. The stability of the hydrocodone in the exemplary bilayer tablet composition that incorporates hydrocodone in a granular form is significantly better than a similar bilayer tablet composition that incorporates hydrocodone in an unprotected powder form.

TABLE 2

Composition of Exemplary Hydrocodone Bilayer Tablet Composition		
Compound	Dry Wt. (% total)	
	IR Layer	SR Layer
Protected hydrocodone granules	2.99%	2.62%
APAP	77.73%	22.73%
MCC	4.82%	26.81%
Hydroxypropyl cellulose	7.71%	1.34%
Cross carmellose sodium	6.00%	
Silicon dioxide	0.50%	0.5%
Magnesium stearate	0.25%	1.0%
Polyethylene oxide polymer		45.0%

EXAMPLES

The following examples demonstrate various aspects of the invention.

Example 1

Incorporation of Protected Oxycodone Granules into Bilayer Tablet Composition

To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan granules into a solid dosage form, the following experiment was conducted.

Powdered oxycodone HCl, microcrystalline cellulose (MCC), and citric acid powder (an antioxidant) were mixed together and charged into a high-shear granulator. An aqueous solution containing pregelatinized starch (PGS) and Na₂EDTA (an antioxidant) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 2% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 µm. The composition of the protected oxycodone granules is summarized in Table 3:

TABLE 3

Composition of Protected Oxycodone Granules	
Compound	Dry Weight (% tot. wt.)
Oxycodone HCl	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

The oxycodone-protected granules were divided into two groups to be incorporated into batches of instant immediate release (IR) granules and into batches of sustained release (SR) granules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed protected oxycodone granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed

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with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 4:

TABLE 4

Composition of IR and SR Granules		
Compound	Dry Wt. (% total wt.)	
	IR Layer	SR Layer
Protected oxycodone granules	16.1%	14.2%
APAP	67.8%	81.2%
MCC	5.0%	
Hydroxypropyl cellulose	8.1%	4.5%
Cross carmellose sodium	3.0%	

The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 5:

TABLE 5

Composition of IR and SR Blends		
Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	99.25%	
SR granules		52.30%
Silicon dioxide	0.50%	0.50%
Magnesium stearate	0.25%	0.10%
MCC		1.20%
Polyethylene oxide polymer		45.00%

The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 29% of the IR blend and about 71% the SR blend by weight.

The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Example 2

Oxidative Stability Assessment of Bilayer Tablet Composition

To assess the effect of incorporating a morphinan in the form of protected granules into a solid dosage therapeutic composition on the oxidative stability of the composition, the following experiment was conducted.

Unprotected bilayer tablets were formed using a process similar to that described in Example 1, except that powdered oxycodone HCl, rather than protected oxycodone granules, were incorporated into the IR and SR granules formed using the fluid bed granulation device. Protected bilayer tablets formed using protected oxycodone granules as described in Example 1 were also obtained. The unprotected bilayer tablets were similar in composition to the protected bilayer tablets, except that the unprotected bilayer tablets lacked antioxidant excipients and oxycodone-protected granules, although the overall oxycodone contents of the two formulations of bilayer tablet were comparable.

A batch of protected bilayer tablets and a batch of unprotected tablets were placed into an environmental chamber and exposed to accelerated stability conditions. In particular, all

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bilayer tablets were kept in the environmental chamber at a temperature of 55° C. and a relative humidity of 80% for a period of six days. For the remainder of the first month and for the duration of a second month, the bilayer tablets were exposed to a temperature of 40° C. and a relative humidity of 75%.

After six days, one month, and two months in the environmental chamber, samples of the protected and unprotected formulations were removed from the chamber and submitted to mass spectrographic analysis to determine the presence of three oxidative degradants of oxycodone: dihydroxy oxycodone, oxycodone n-oxide, and 10-hydroxy oxycodone. The results of these analyses are summarized in Table 6 below:

TABLE 6

Oxidative Stability of Unprotected vs. Protected Formulations of Bilayer Tablets								
Degradation Conditions			Amount of Degradant Formed (% weight of oxycodone)					
			Di-hydroxy oxycodone		10-hydroxy oxycodone		Oxycodone n-oxide	
Time (days)	Temp. (° C.)	Relative Humidity (%)	Not Protected	Protected	Not Protected	Protected	Not Protected	Protected
6	55	80	0.20	0.00	0.04	0.00	0.12	0.03
30	40	75	0.05	0.01	0.01	0.00	0.12	0.01
60	40	75	0.11	0.02	0.03	0.00	0.21	0.03

The protected formulation of the bilayer tablets that incorporated the oxycodone-protected granules had significantly lower levels of all degradants after exposure to all environmental conditions. No 10-hydroxy oxycodone was measured at any environmental condition for the protected formulation of the bilayer tablet.

The results of this experiment demonstrated that the formation of oxidative degradants of oxycodone was significantly inhibited by the incorporation of the oxycodone in the form of protected granules. In particular, the bilayer tablets formed using the protected oxycodone granules were significantly more stable than similar bilayer tablets formed using unprotected oxycodone powder.

Example 3

Effect of Granule Composition on Oxidative Stability

To assess the effect of various granule compositions on the oxidative stability of the morphinan encapsulated in the granules, the following experiment was conducted.

Granules containing oxycodone and various combinations of excipients were formed using methods similar to those described in Example 1. The specific compositions of the granules are summarized in Table 7:

TABLE 7

Composition of IR and SR Granules					
Compound	Granule Composition (% w/w)				
	1	2	3	5	6
Oxycodone	30	30	30	30	30
MCC	65	64.95	62.2	64.95	62.2
HPC	5	4.6	4.6		
BHA		0.05		0.05	
EDTA		0.4	0.4	0.4	0.4

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TABLE 7-continued

Composition of IR and SR Granules					
Compound	Granule Composition (% w/w)				
	1	2	3	5	6
Ascorbic Acid			2.8		2.8
PGS				4.6	4.6

For granule compositions 1, 2, and 3 the HPC and EDTA were dissolved in a granulation solution and applied to a dry mixture of the remaining ingredients. For granule composi-

tions 5 and 6, the PGS and EDTA were dissolved in a granulations solution and applied to a dry mixture of the remaining ingredients.

The resulting granules were stored at accelerated stability conditions for a period of 4 weeks at 40° C. and 75% relative humidity. Samples of the granules were taken just before storage and after one, two, and four weeks of storage at accelerated stability conditions and subjected to mass spectrographic analysis as described in Example 2 to determine the presence of oxidative degradants of oxycodone. The results of the analyses of the samples taken after four weeks of storage are summarized in Table 8 below:

TABLE 8

Oxidative Stability of Granule Formulations		
Composition	Impurity After 4 Weeks at Accelerated Degradation Conditions (% wt of oxycodone)	
	6-a-Oxycodol	Noroxo
1	0.11	0.01
2	0.11	0.02
3	0.33	0.13
5	0.11	0.00
6	0.29	0.14

The impurities for granule compositions 1, 2, and 5 were all of comparable low amounts, indicating that the granulation of the oxycodone resulted in a protective effect from oxidative degradation. This protective effect was achieved even in granule composition 1, which did not include any antioxidant excipients. However, granule compositions 3 and 6, which contained ascorbic acid, resulted in much higher levels of oxidative impurities after 4 weeks of storage at accelerated stability conditions, indicating that the ascorbic acid may produce oxidative products that result in the long-term degradation of the oxycodone.

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The results of this experiment demonstrated the protective effect of granulation against the oxidative degradation of oxycodone, so long as ascorbic acid was not included in the granule composition.

Example 4

Effect of Granulation Composition on Oxidative
Stability of Solid Dose Oxycodone/APAP
Formulations

To assess the effect of encapsulation on the oxidative stability of the morphinan in various solid dose formulations, the following experiment was conducted.

Solid dose tablets were formed using the methods described in Example 2. The solid dose tablets contained the oxycodone either in the protected granular form described in Example 3, or as the same ingredients in a powdered form rather than as granules. In both cases, the oxycodone and excipients were combined with APAP and polyethylene oxide (PEO) polymer. Each tablet contained 10% of the oxycodone granule compositions described in Example 3, in either granulated or powdered form, 46.8% APAP, and 43.2% PEO polymer on a weight basis.

The protected and unprotected tablet formulations were stored at accelerated stability conditions for a period of 4 weeks at 40° C. and 75% relative humidity. Samples of the tablets were taken just before storage and after one, two, and four weeks of storage at accelerated stability conditions and subjected to mass spectrographic analysis as described in Example 2 to determine the presence of oxidative degradants of oxycodone. The results of these analysis of the samples taken after four weeks of storage are summarized in Table 9 below:

TABLE 9

Effect of Granulation on Oxidative Stability of Tablet Formulations				
Composition Combined	Impurity After 4 Weeks at Accelerated Degradation Conditions (% wt of oxycodone)			
	with APAP		Noroxy	
	6-a-Oxycodol			
and PEO Polymer	Protected granules	Unprotected	Protected Granules	Unprotected
1	0.20	.74	0.03	.27
2	0.22	.51	0.05	.28
3	0.60	1.25*	0.11	.14*
5	0.17	.49	0.01	.18

*measured at two weeks after storage

All of the protected tablet formulations, in which the oxycodone was granulated using methods similar to those described in Example 1 formed significantly lower levels of impurities after storage for 4 weeks at accelerated stability conditions compared to tablets containing non-granulated oxycodone and the same excipients

The results of this experiment demonstrated that granulating the oxycodone and excipients prior to incorporating the granules in a tableting process resulted in tablets with superior stability compared to tablets formed using the same oxycodone and excipients in a loose powder form, independent of the particular composition of excipients in the formulation.

Example 5

Incorporation of Protected Oxycodone Granules into
Bilayer Tablet Composition

To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan

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granules into a solid dosage form, the following experiment was conducted to prepare a 7.5 mg oxycodone/325 mg acetaminophen tablet.

Powdered oxycodone HCl, microcrystalline cellulose (MCC), pregelatinized starch (PGS), Na₂EDTA (an antioxidant), and citric acid powder (an antioxidant) were charged into a high-shear granulator and mixed together. An aqueous solution containing pregelatinized starch (PGS) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 5% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 µm after milling. The composition of the oxycodone-protected granules is summarized in Table 10:

TABLE 10

Composition of Protected Oxycodone Granules	
Compound	Dry Weight (% tot. wt.)
Oxycodone HCl	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

The oxycodone-protected granules were divided into two groups to be incorporated into batches of immediate release (IR) granules and into batches of sustained release (SR) granules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed oxycodone-protected granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 11:

TABLE 11

Composition of IR and SR Granules		
Compound	Dry Wt. (% total wt.)	
	IR Granules	SR Granules
Protected oxycodone granules	3.10%	9.79%
APAP	80.65%	84.81%
MCC	5.0%	
Hydroxypropyl cellulose	8.0%	5.0%
Cross carmellose sodium	3.0%	
Silicon Dioxide	0.25%	0.4%

The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 12:

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TABLE 12

Composition of IR and SR Blends		
Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	96.38%	
SR granules		26.80%
Croscarmellose Sodium	3.11%	
Silicon dioxide	0.26%	0.39%
Magnesium stearate	0.25%	1.0%
MCC		26.81%
Polyethylene oxide polymer		45.00%

The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 23% of the IR blend and about 77% the SR blend by weight.

The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Example 6

Incorporation of Protected Hydrocodone Granules into Bilayer Tablet Composition

To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan granules into a solid dosage form, the following experiment was conducted to prepare a 7.5 mg hydrocodone/325 mg acetaminophen tablet.

Powdered hydrocodone bitartrate, microcrystalline cellulose (MCC), pregelatinized starch (PGS) and citric acid powder (an antioxidant) were mixed together and charged into a high-shear granulator. An aqueous solution containing pregelatinized starch (PGS) and Na₂EDTA (an antioxidant) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 5% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 μ m after milling. The composition of the protected hydrocodone granules is summarized in Table 13:

The hydrocodone-protected granules were divided into two groups to be incorporated into batches of immediate release (IR) granules and into batches of sustained release (SR) granules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed protected hydrocodone granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 14:

TABLE 13

Composition of Protected Hydrocodone Granules	
Compound	Dry Weight (% tot. wt.)
Hydrocodone bitartrate	30.0%
MCC	63.6%
PGS	4.0%

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TABLE 13-continued

Composition of Protected Hydrocodone Granules	
Compound	Dry Weight (% tot. wt.)
Na ₂ EDTA	0.4%
Citric acid	2.0%

TABLE 14

Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
Protected hydrocodone granules	3.10%	9.79%
APAP	80.65%	84.81%
MCC	5.0%	
Hydroxypropyl cellulose	8.0%	5.0%
Cross carmellose sodium	3.0%	
Silicon Dioxide	0.25%	0.4%

The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 15:

TABLE 15

Composition of IR and SR Blends		
Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	96.38%	
SR granules		26.80%
Croscarmellose Sodium	3.11%	
Silicon dioxide	0.26%	0.39%
Magnesium stearate	0.25%	1.0%
MCC		26.81%
Polyethylene oxide polymer		45.00%

The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 23% of the IR blend and about 77% the SR blend by weight.

The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Having described the invention in detail, it will be apparent that modifications and variations are possible. Those of skill in the art should, in light of the present disclosure, appreciate that many changes could be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth is to be interpreted as illustrative and not in a limiting sense.

What is claimed is:

1. A granule substantially resistant to oxidative degradation of oxycodone, the granule comprising an interior region substantially comprising oxycodone and an exterior region substantially comprising at least one excipient selected from the group consisting of a binder, a filler, an antioxidant, a chelating agent, and combinations thereof, wherein the exterior region surrounds the interior region, and wherein the granule contains less than about 0.5% w/w of the total mass of oxycodone of each of any one or more of a degradant selected

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from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

2. The granule of claim 1, wherein less than about 20% of the total weight of the oxycodone in the granule is exposed on the surface of the granule.

3. The granule of claim 1, further comprising at least one additional excipient selected from the group consisting of pH adjusting agents, antimicrobial agents, and combinations thereof.

4. The granule of claim 1, wherein the granule comprises microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid.

5. The granule of claim 1, wherein the oxycodone has a d₉₀ that is less than the d₉₀ of the excipient.

6. The granule of claim 5, wherein the d₉₀ of the oxycodone is less than about 80% of the d₉₀ of the excipient.

7. The granule of claim 1, wherein the oxycodone is oxycodone hydrochloride.

8. The granule of claim 1, further comprising at least one additional active pharmaceutical ingredient.

9. The granule of claim 8, wherein the at least one additional active pharmaceutical ingredient comprises acetaminophen.

10. The granule of claim 1, further comprising a hydrophilic polymer.

11. The granule of claim 10, wherein the hydrophilic polymer is selected from the group consisting of cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose ethers, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, nitrocellulose, crosslinked starch, agar, casein, chitin, collagen, gelatin, maltose, mannitol, maltodextrin, pectin, pullulan, sorbitol, xylitol, polysaccharides, ammonia alginate, sodium alginate, calcium alginate, potassium alginate, propylene glycol alginate, alginate sodium carmellose, calcium carmellose, carrageenan, fucoidan, furcellaran, arabicgum, carrageensgum, ghaftigum, guar gum, karayagum, locust beangum, okragum, tragacanthum, scleroglucangum, xanthangum, hypnea, laminaran, acrylic polymers, acrylate polymers, carboxyvinyl polymers, copolymers of maleic anhydride and styrene, copolymers of maleic anhydride and ethylene, copolymers of maleic anhydride propylene or copolymers of maleic anhydride isobutylene), crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, diesters of polyglucan, polyacrylamides, polyacrylic acid, polyamides, polyethylene glycols, polyethylene oxides, poly(hydroxyalkyl methacrylate), polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, polystyrenes, polyvinylpyrrolidone, anionic and cationic hydrogels, and combinations thereof.

12. The granule of claim 1, further comprising a hydrophobic polymer.

13. The granule of claim 12, wherein the hydrophobic polymer is selected from the group consisting of cellulose acetate butyrate, cellulose acetate ethylcarbamate, cellulose acetate heptanoate, cellulose acetate methylcarbamate, cellulose acetate octanoate, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate succinate, cellulose acetate trimaletate, cellulose acetaldehyde dimethyl acetate, cellulose butyrate, cellulose dimethylaminoacetate, cellulose disuccinate, cellulose dipalmitate, cellulose dicaprylate, cellulose propionate, cellulose propionate succinate, cellulose trioctanoate, cellulose tripropionate, cellulose trimellitate, cellulose tripalmitate, cellulose trivalerate, cellulose valerate palmitate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, ethylhydroxy ethylcellulose, hydroxy propyl methylcellulose

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phthalate, methyl cellulose, methyl ethyl cellulose, propyl cellulose, sodium carboxymethyl starch, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, methacrylic acid copolymers, methacrylic acid ester copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylate), poly(methacrylate), poly(methyl methacrylate), poly(ethylacrylate), poly(ethyl methacrylate), poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, ammonio methacrylate copolymers, lecithins, aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, hydrogenated vegetable oil, 12-hydroxystearyl alcohol, glyceryl monopalmitate, glyceryl dipalmitate, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, myristyl alcohol, stearic acid, stearyl alcohol, polyethyleneglycols, zein, shellac, bee's wax, carnauba wax, glyceryl behenate, Japan wax, paraffin, spermaceti, synthetic waxes, and combinations thereof.

14. A granule substantially resistant to oxidative degradation of hydrocodone, the granule comprising hydrocodone, and at least one excipient chosen from a binder, a filler, an antioxidant, a chelating agent, and combinations thereof, wherein the granule contains less than about 0.5% w/w of the total mass of hydrocodone of each of any one or more of a degradant selected from hydrocodone-n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

15. A granule substantially resistant to oxidative degradation of a morphinan, the granule prepared by a process comprising granulating a mixture comprising the morphinan and at least one excipient chosen from a binder, a filler, an antioxidant, a chelating agent, and combinations thereof in a manner such that substantially all of the morphinan is surrounded by the at least one excipient, thereby forming the morphinan-protected granule; when the morphinan is oxycodone, the granule contains less than about 0.5% w/w of the total mass of oxycodone of one or more of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide, after being stored for 6 months at 40° C. and 75% relative humidity, and when the morphinan is hydrocodone, the granule contains less than about 0.5% w/w of the total mass of hydrocodone of each of one or more of a degradant selected from hydrocodone-n-oxide and hydrocodone aldol dimer, after being stored for 6 months at 40° C. and 75% relative humidity.

16. The granule of claim 15, wherein the morphinan is oxycodone.

17. The granule of claim 16, wherein the granule contains less than about 0.5% w/w of the total mass of oxycodone of each of any one or more of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide thereof after being stored for 6 months at 40° C. and 75% relative humidity.

18. The granule of claim 15, wherein the morphinan is hydrocodone.

19. The granule of claim 15, wherein the granule comprises microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid.

20. A pharmaceutical composition comprising a plurality of oxycodone-containing granules substantially resistant to oxidative degradation of oxycodone and at least one pharmaceutically acceptable carrier, the plurality of granules comprising an interior region substantially comprising oxycodone and an exterior region substantially comprising at least one excipient, wherein the pharmaceutical composition contains less than about 0.5% w/w of the total mass of oxycodone of each of any one or more of a degradant selected from

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10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

21. The pharmaceutical composition of claim 20, wherein less than about 30% of the total weight of the oxycodone in the oxycodone-containing granules is exposed on the surface of the granules.

22. The pharmaceutical composition of claim 20, wherein the at least one pharmaceutically acceptable carrier is incompatible with oxycodone.

23. The pharmaceutical composition of claim 22, wherein the at least one pharmaceutically acceptable carrier is a polyethylene oxide polymer.

24. The pharmaceutical composition of claim 20, further comprising at least one additional active pharmaceutical ingredient.

25. The pharmaceutical composition of claim 24, wherein the at least one additional active pharmaceutical ingredient comprises acetaminophen.

26. The pharmaceutical composition of claim 25, further comprising a plurality of tablet granules comprising the oxycodone-containing granules, the acetaminophen, and at least one additional excipient.

27. The pharmaceutical composition of claim 26, wherein the at least one additional excipient is a polyethylene oxide polymer.

28. The pharmaceutical composition of claim 26, wherein the at least one pharmaceutically acceptable carrier is a polyethylene oxide polymer.

29. A pharmaceutical composition comprising a plurality of hydrocodone-containing granules substantially resistant to oxidative degradation of hydrocodone and at least one pharmaceutically acceptable carrier, the plurality of granules comprising hydrocodone and at least one excipient, wherein the pharmaceutical composition contains less than about 0.5% w/w of the total mass of hydrocodone of each of any one or more of a degradant selected from hydrocodone-n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

30. The pharmaceutical composition of claim 29, wherein the hydrocodone-protected granules have a physical structure that reduces the amount of hydrocodone exposed on the surface of the granules.

31. The pharmaceutical composition of claim 29, wherein the pharmaceutically acceptable carrier is incompatible with hydrocodone.

32. The pharmaceutical composition of claim 29, further comprising at least one additional active pharmaceutical ingredient.

33. A solid dosage pharmaceutical composition comprising a plurality of oxycodone-protected granules and acetaminophen, the composition prepared by a process comprising:

- (a) granulating a first mixture comprising the oxycodone and at least one excipient to form the plurality of oxyc-

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odone-protected granules, wherein the oxycodone in the oxycodone-protected granules is substantially resistant to oxidative degradation;

- (b) granulating a second mixture in the presence of a granulation fluid, the second mixture comprising the plurality of oxycodone-protected granules, the acetaminophen, and at least one additional excipient to form a plurality of tablet granules; and

- (c) blending the plurality of tablet granules with a release-controlling polymer comprising a polyethylene oxide polymer and optionally at least one carrier to form the solid dosage pharmaceutical composition comprising a sustained release layer; wherein the granule contains less than about 0.5% w/w of the total mass of oxycodone of one or more of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide, after being stored for 6 months at 40° C. and 75% relative humidity.

34. The solid dosage pharmaceutical composition of claim 33, further comprising step (d) which includes granulating a third mixture in the presence of a granulation fluid, the third mixture comprising oxycodone-protected granules, acetaminophen, and at least one additional excipient to form a plurality of immediate release granules, and step (e) blending the immediate release granules with at least one excipient to form an immediate release layer.

35. The pharmaceutical composition of claim 33, wherein less than about 30% of the total weight of the oxycodone in the tablet granules is exposed on the surface of the granules.

36. A granule prepared by a process comprising:

- (a) granulating a first mixture comprising oxycodone and at least one excipient to form a first granulated mixture;
- (b) granulating a second mixture in the presence of a granulation fluid, the second mixture comprising the first granulated mixture, acetaminophen, and at least one additional excipient to form a second granulated mixture;

wherein the first granulated mixture and the second granulated mixture comprise the granule; and

wherein the granule contains less than about 0.5% w/w of the total mass of oxycodone of each of any one or more of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

37. The granule of claim 36, further comprising blending the granule with a release-controlling polymer.

38. The granule of claim 37, wherein the release-controlling polymer is a polyethylene oxide polymer

39. The granule of claim 36, further comprising blending the granule with a lubricant.

* * * * *

EXHIBIT B

US008658631B1

(12) **United States Patent**
Devarakonda et al.

(10) **Patent No.:** **US 8,658,631 B1**
(45) **Date of Patent:** ***Feb. 25, 2014**

(54) **COMBINATION COMPOSITION
COMPRISING OXYCODONE AND
ACETAMINOPHEN FOR RAPID ONSET AND
EXTENDED DURATION OF ANALGESIA**

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USPC **514/183**

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(56) References Cited

U.S. PATENT DOCUMENTS

4,713,243	A	12/1987	Schiraldi et al.
4,851,226	A	7/1989	Julian et al.
4,894,236	A	1/1990	Jang et al.
4,996,058	A	2/1991	Sinnreich
5,075,114	A	12/1991	Roche
5,266,331	A	11/1993	Oshlack et al.
5,336,691	A	8/1994	Raffa et al.
5,478,577	A	12/1995	Sackler et al.
5,508,042	A	4/1996	Oshlack et al.
5,549,912	A	8/1996	Oshlack et al.
5,582,837	A	12/1996	Shell
5,626,874	A	5/1997	Conte et al.
5,656,295	A	8/1997	Oshlack et al.
5,672,360	A	9/1997	Sackler et al.
5,783,212	A	7/1998	Fassihi et al.
5,866,161	A	2/1999	Childers et al.
5,876,759	A	3/1999	Gowan, Jr.
5,891,471	A	4/1999	Miller et al.
5,945,123	A	8/1999	Hermelin
5,945,125	A	8/1999	Kim
5,958,459	A	9/1999	Chasin et al.
5,965,161	A	10/1999	Oshlack et al.
5,965,163	A	10/1999	Miller et al.

5,965,167	A	10/1999	Sanghvi et al.
5,968,551	A	10/1999	Oshlack et al.
5,972,389	A	10/1999	Shell et al.
5,980,882	A	11/1999	Eichman
6,024,982	A	2/2000	Oshlack et al.
6,068,855	A	5/2000	Leslie et al.
6,071,208	A	6/2000	Koivunen
6,103,219	A	8/2000	Sherwood et al.
6,103,261	A	8/2000	Chasin et al.
6,126,969	A	10/2000	Shah et al.
6,143,322	A	11/2000	Sackler et al.
6,210,714	B1	4/2001	Oshlack et al.
6,245,357	B1	6/2001	Edgren et al.
6,251,430	B1	6/2001	Zhang et al.
6,254,887	B1	7/2001	Miller et al.
6,340,475	B2	1/2002	Shell et al.
6,372,254	B1	4/2002	Ting et al.
6,375,957	B1	4/2002	Kaiko et al.
6,387,404	B2	5/2002	Oshlack et al.
6,488,962	B1	12/2002	Berner et al.
6,488,963	B1	12/2002	McGinity et al.
6,500,459	B1	12/2002	Chhabra et al.
6,599,529	B1	7/2003	Skinhoj et al.
6,635,280	B2	10/2003	Shell et al.
6,667,060	B1	12/2003	Vandecruys et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	159852	10/1985
EP	1140026	6/2000

(Continued)

OTHER PUBLICATIONS

Ward et al., Modeling the economic and health consequences of
managing chronic osteoarthritis pain with opioids in Germany: com-
parison of extended release oxycodone and OROS hydromorphone,
Current Medical Research and Opinion, 23(10):2333-2345, 2007.*
Koizumi et al., Efficacy and Tolerability of Cancer Pain Management
with Controlled-release Oxycodone Tablets in Opioid-naïve Cancer
Pain Patients, Starting with 5 mg Tablets, Jpn J Clin Oncol,
34(10):608-614, 2004.*
Gammaitoni et al., Effectiveness and Safety of New Oxycodone/
Acetaminophen Formulations With Reduced Acetaminophen for the
Treatment of Low Back Pain, Pain Medicine, 4(1):21-30, 2003.*

(Continued)

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(57) ABSTRACT

The present disclosure provides an extended release pharma-
ceutical composition comprising oxycodone and acetami-
nophen that provides a rapid onset of analgesia, and reduced
levels of acetaminophen near the end of the dosing interval.
Also provided are methods for reducing the risk of acetami-
nophen-induced hepatic damage in a subject being treated
with an acetaminophen containing composition, as well as
methods for treating pain in a subject in need thereof.

30 Claims, 49 Drawing Sheets
(29 of 49 Drawing Sheet(s) Filed in Color)

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(56)

References Cited

U.S. PATENT DOCUMENTS

6,682,759	B2	1/2004	Lim et al.	2007/0259045	A1	11/2007	Mannion et al.
6,696,066	B2	2/2004	Kaiko et al.	2007/0275065	A1	11/2007	Oshlack et al.
6,706,281	B2	3/2004	Oshlack et al.	2007/0281018	A1	12/2007	Qiu et al.
6,723,340	B2	4/2004	Gusler et al.	2008/0020039	A1	1/2008	Parikh et al.
6,730,321	B2	5/2004	Ting et al.	2008/0031901	A1	2/2008	Qiu et al.
6,733,783	B2	5/2004	Oshlack et al.	2008/0031963	A1	2/2008	Sackler et al.
6,797,283	B1	9/2004	Edgren et al.	2008/0044482	A1	2/2008	Oshlack et al.
6,852,336	B2	2/2005	Hunter et al.	2008/0057122	A1	3/2008	Toney-Parker et al.
6,902,742	B2	6/2005	Devane et al.	2008/0113025	A1	5/2008	Devane et al.
7,074,430	B2	7/2006	Miller et al.	2008/0132532	A1	6/2008	Wright et al.
7,201,920	B2	4/2007	Kumar et al.	2008/0138422	A1	6/2008	Staniforth
7,374,781	B2	5/2008	Zhang et al.	2008/0220062	A1	9/2008	Ashton
7,405,238	B2	7/2008	Markey et al.	2009/0022798	A1	1/2009	Rosenberg et al.
7,413,751	B2	8/2008	Devane et al.	2009/0028941	A1	1/2009	Cowles et al.
7,438,927	B2	10/2008	Berner et al.	2009/0068269	A1	3/2009	Oshlack et al.
7,514,100	B2	4/2009	Oshlack et al.	2009/0081290	A1	3/2009	McKenna et al.
7,674,799	B2	3/2010	Chapman et al.	2009/0149479	A1	6/2009	Jenkins et al.
7,674,800	B2	3/2010	Chapman et al.	2009/0155357	A1	6/2009	Muhuri
7,683,072	B2	3/2010	Chapman et al.	2009/0175937	A1	7/2009	Rahmouni et al.
7,691,873	B2	4/2010	Duncalf et al.	2009/0202629	A1	8/2009	Oshlack et al.
7,776,314	B2	8/2010	Bartholomaeus et al.	2009/0304793	A1	12/2009	Boehm
7,846,476	B2	12/2010	Oshlack et al.	2009/0306119	A1	12/2009	Keane
7,897,172	B2	3/2011	Oasem et al.	2009/0311320	A1	12/2009	Oury et al.
7,939,543	B2	5/2011	Kupper	2009/0317355	A1	12/2009	Roth et al.
7,943,170	B2	5/2011	Chan et al.	2009/0324714	A1	12/2009	Liu et al.
7,976,870	B2	7/2011	Berner et al.	2010/0010030	A1	1/2010	Jain et al.
8,075,872	B2	12/2011	Arkenau-Maric et al.	2010/0015222	A1 *	1/2010	Han et al. 424/468
8,309,060	B2	11/2012	Bartholomaeus et al.	2010/0034876	A1	2/2010	Oshlack et al.
8,337,888	B2	12/2012	Wright et al.	2010/0040681	A1	2/2010	Park et al.
2001/0008639	A1	7/2001	Oshlack et al.	2010/0092570	A1	4/2010	Oshlack et al.
2002/0018810	A1	2/2002	Oshlack et al.	2010/0168148	A1	7/2010	Wright et al.
2002/0058050	A1	5/2002	Sackler et al.	2010/0172974	A1	7/2010	Oshlack et al.
2002/0192277	A1	12/2002	Oshlack et al.	2010/0172989	A1	7/2010	Roth et al.
2003/0035837	A1	2/2003	Sackler et al.	2010/0196425	A1	8/2010	Cruz et al.
2003/0044466	A1	3/2003	Markey et al.	2010/0196471	A1	8/2010	Jain et al.
2003/0091635	A1	5/2003	Baichwal et al.	2010/0196474	A1	8/2010	Han et al.
2003/0092724	A1	5/2003	Kao et al.	2010/0216829	A2	8/2010	Kumar et al.
2003/0099704	A1	5/2003	Oshlack et al.	2010/0221293	A1	9/2010	Cruz et al.
2003/0104062	A1	6/2003	Berner et al.	2010/0239662	A1	9/2010	Rahmouni et al.
2004/0096500	A1	5/2004	Oshlack et al.	2010/0260833	A1	10/2010	Bartholomaeus et al.
2004/0105887	A1	6/2004	Oshlack et al.	2011/0020451	A1	1/2011	Bartholomaeus et al.
2004/0131671	A1	7/2004	Zhang et al.	2011/0038927	A1	2/2011	Oshlack et al.
2004/0156899	A1	8/2004	Louie-Helm et al.	2011/0038930	A1	2/2011	Barnscheid et al.
2005/0013863	A1	1/2005	Lim et al.	2011/0052685	A1	3/2011	Hou et al.
2005/0020613	A1	1/2005	Boehm et al.	2011/0077238	A1	3/2011	Leech et al.
2005/0031546	A1	2/2005	Bartholomaeus et al.	2011/0117196	A1	5/2011	Gordon
2005/0089570	A1	4/2005	Cruz et al.	2011/0118189	A1	5/2011	Farr et al.
2005/0106249	A1	5/2005	Hwang et al.	2011/0129507	A1	6/2011	Cruz
2005/0112195	A1	5/2005	Cruz et al.	2011/0150969	A1	6/2011	Shah et al.
2005/0158382	A1	7/2005	Cruz et al.	2011/0150970	A1	6/2011	Shah et al.
2005/0165038	A1	7/2005	Gordon	2011/0150971	A1	6/2011	Shah et al.
2005/0232987	A1	10/2005	Srinivasan et al.	2011/0150989	A1	6/2011	Park et al.
2005/0266032	A1	12/2005	Srinivasan et al.	2011/0150990	A1	6/2011	Shah et al.
2005/0267189	A1	12/2005	Gao et al.	2011/0150991	A1	6/2011	Shah et al.
2006/0002860	A1	1/2006	Bartholomaeus et al.	2011/0159046	A1	6/2011	Cruz
2006/0057210	A1	3/2006	Oshlack et al.	2011/0166171	A1	7/2011	Qiu et al.
2006/0099255	A1	5/2006	Oshlack et al.	2011/0177168	A1	7/2011	Chan et al.
2006/0165791	A1	7/2006	Oshlack et al.	2011/0195116	A1	8/2011	Hobbs et al.
2006/0193782	A1	8/2006	Bartholomaeus et al.	2011/0195989	A1	8/2011	Rudnic et al.
2006/0205752	A1	9/2006	Whitehead	2011/0207762	A1	8/2011	Chapman et al.
2006/0240105	A1	10/2006	Devane et al.	2011/0212173	A1	9/2011	Young et al.
2006/0251721	A1	11/2006	Cruz et al.	2011/0229526	A1	9/2011	Rosenberg et al.
2006/0263436	A1	11/2006	Baert et al.	2011/0229533	A1	9/2011	Edgren et al.
2006/0269604	A1	11/2006	Sackler et al.	2011/0262532	A1	10/2011	Oshlack et al.
2006/0292214	A1	12/2006	Jenkins et al.	2011/0287095	A1	11/2011	Park et al.
2007/0020335	A1	1/2007	Chen et al.	2011/0301129	A1	12/2011	Berner et al.
2007/0048228	A1	3/2007	Arkenau-Maric et al.	2011/0318392	A1	12/2011	Cruz et al.
2007/0059359	A1	3/2007	Backensfeld et al.	2012/0321713	A1	12/2012	Han et al.
2007/0128279	A1	6/2007	Edgren et al.				
2007/0183980	A1	8/2007	Arkenau-Maric et al.				
2007/0184112	A1	8/2007	Wong et al.				
2007/0190142	A1	8/2007	Breitenbach et al.				
2007/0207200	A1	9/2007	Plachetka et al.				
2007/0237833	A1	10/2007	Sackler et al.				
2007/0259033	A1	11/2007	Cruz				

FOREIGN PATENT DOCUMENTS

WO	9718814	5/1997
WO	9855107	12/1998
WO	03024426	3/2003
WO	2005013863	2/2005
WO	2005030182	4/2005
WO	2006022759	3/2006
WO	2006071208	7/2006
WO	2008015221	2/2008

US 8,658,631 B1

Page 3

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2009049405	4/2009
WO	2009076764	6/2009
WO	2009114648	9/2009
WO	2009135846	11/2009
WO	2010032128	3/2010
WO	2010069050	6/2010
WO	2010078486	7/2010
WO	2010141505	12/2010
WO	2011009603	1/2011
WO	2011009604	1/2011
WO	2011068723	6/2011
WO	2011077451	6/2011
WO	2011106416	9/2011
WO	2012007159	1/2012

OTHER PUBLICATIONS

Aulton M. E. "Aulton's Pharmaceutics: The Design and Manufacture of Medicines," Elsevier Limited, Oxford, Third Edition, 2007, pp. 270-278.

Prinderre et al., "Advances in Gastro Retentive Drug-Delivery Systems," Expert Opin. Drug. Deliv., 8(9), p. 1189-1203 (Sep. 2011).

Berner et al., "Case Studies in Swelling Polymeric Gastric Retentive Tablets," Expert Opin. Drug. Deliv., 3(4), p. 541-548 (Jul. 2006).

Gralise Prescribing Information, 24 pages.

Glumetza Prescribing Information, 10 pages.

Tylenol® Professional Product Information, 62 pages.

U.S. Appl. No. 13/360,595, filed Jan. 27, 2012, Hien-Hsuan Han et al.

U.S. Appl. No. 13/473,571, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,578, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,584, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,586, filed May 16, 2012, Devarakonda et al.

Banfai B. Ganzler K, Kemeny S. Content uniformity and assay requirements in current regulations. J Chromatogr A. Jul. 13, 2007;1156(1-2):206-12. Epub Nov. 15, 2006.

Zhu Y, Shah NH Malick AW, Infeld MH, McGinity JW. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int J Pharm. Jul. 25, 2002; 241(2):301-10.

Nimmo, W.S. et al., "Inhibition of Gastric Emptying and Drug Absorption by Narcotic Analgesics", Br. J. Clin. Pharmac., 2:509-513 (1975).

Altat S A et al., "Bead Compacts II. Evaluation of Rapidly Disintegrating Nonsegregating Compressed Bead Formulations"; Drug Development and Industrial Pharmacy, New York, NY, US, vol. 25, No. 5, May 1, 1999; pp. 635-642.

International Search Report from Application No. PCT/US2010/061400 with a mailing date of Nov. 25, 2011.

Endo Pharmaceuticals Package Insert for Percocet (Oxycodone and Acetaminophen Tablets, USP); pp. 1-17.

www.fda.gov/Drugs/DrugSafety/ucm239821.htm; U.S. Department of Health & Human Services; FDA Drugs Safety Communication: Prescription Acetaminophen Products to be Limited to 325mg per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure; pp. 1-5.

Tylenol Professional Product Information(2010); McNeil Consumer Healthcare; pp. 1-59.

Oxycontin Description and Patient Information; pp. 1-32.

Cooperman et al.; "A Novel Extended-Release Formulation of Oxycodone/Acetaminophen with Abuse Deterrent Properties"; Abstract; 2pgs.

Khosla et al. "The effect of tablet size on the gastric emptying of non-disintegrating tablets" (1990), International Journal of Pharmaceutics, 62, R9-R11.

Khosla et al. Gastrointestinal transit of non-disintegrating tablets in fed subjects (1989), International Journal of Pharmaceutics, 53, 107-117.

Khosla et al. "The gastrointestinal transit of a controlled release formulation of indomethacin", (1990), International Journal of Pharmaceutics, 60, 191-196.

Brzeznicza et al. "Dynamics of Glutathione Levels in Liver and Indicatory Enzymes in Serum in Acetaminophen Intoxication in Mice" (1989) Polish Journal of Occupational Medicine, vol. 2, No. 1, pp. 15-22.

Gammaitoni et al. "Randomized, Double-Blind, Placebo-Controlled Comparison of the Analgesic Efficacy of Oxycodone 10 mg/Acetaminophen 325 mg versus Controlled-Release Oxycodone 20 mg in Postsurgical Pain", (2003), J. Clin. Pharmacol, 43: pp. 296-304.

Moller et al. "Time to Onset of Analgesia and Analgesic Efficacy of Effervescent Acetaminophen," (2000); J. Clin. Pharmacol. 40: 370-378.

Nielsen et al. "Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol", (1992), Eur. J. Clin Pharmacol 42: 261-264.

James et al, "Acetaminophen-Induced Hepatotoxicity", The American Society for Pharmacology and Experimental Therapeutics, (2003), vol. 31, No. 12, pp. 1499-1506.

Mirochnitchenko et al. "Acetaminophen Toxicity", The American Society for Biochemistry and Molecular Biology, Inc., (1999), vol. 274, No. 15, pp. 10349-10355.

Dart et al. "Acetaminophen Poisoning: An Evidence-Based Consensus Guideline for Out-of-Hospital Management", (2006), Clinical Toxicology; 44: pp. 1-18.

Bolesta et al. "Hepatotoxicity Associated with Chronic Acetaminophen Administration in Patients without Risk Factors", (2002), The Annals of Pharmacotherapy; Feb. 2002, Vo. 36, pp. 331-333.

Rinaldi et al. "Minireview Reactive Intermediates and the Dynamics of Glutathione Transferases" (2002); The American Society for Pharmacology and Experimental Therapeutics; 30:pp. 1053-1058.

Rumack et al. "Acetaminophen Hepatotoxicity: The First 35 Years", Clinical Toxicology, (2002); 40(1), 3-20.

Bartels et al., "Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial"; (2008); Clinical Toxicology; 46: 243-249.

Corcoran et al. "Role of Glutathione in Prevention of Acetaminophen-Induced Hepatotoxicity by N-Acetyl-L-Cysteine in Vivo: Studies with N-Acetyl-D-Cysteine in Mice"; The Journal of Pharmacology and Experimental Therapeutics; (1986); vol. 238, No. 1; pp. 54-61.

Davis et al. "Species Differences in Hepatic Glutathione Depletion, Covalent Binding and Hepatic Necrosis after Acetaminophen", Life Sciences, vol. 14, pp. 2099-2109.

Mitchell et al. "Acetaminophen-Induced Hepatic Necrosis. IV. Protective Role of Glutathione", The Journal of Pharmacology and Experimental Therapeutics; (1973), vol. 187, No. 1, pp. 211-217.

Kaplowitz et al. "Drug-Induced Liver Disease" (2003); Marcel Dekker, pp. 287-325 and pp. 345-375.

Skoglund et al. "Efficacy of paracetamol-esterified methionine versus cysteine or methionine on paracetamol-induced hepatic GSH depletion and plasma ALT level in mice", Biochem Pharmacol 35; 3071-3075, (1986).

Talukder et al.; "Gastroretentive Delivery Systems: A Mini Review"; Drug Development and Industrial Pharmacy; 2004; pp. 1019-1028; vol. 30, No. 10.

Hou et al.; "Gastric Retentive Dosage Forms: A Review"; Critical Review in Therapeutic Drug Carrier Systems; 2003; pp. 462-497; 20(6).

Streubel et al. "Drug delivery to the upper small intestine window using gastroretentive technologies"; ScienceDirect; 2006; pp. 501-508; 6.

Streubel et al. "Gastroretentive drug delivery systems"; Expert Opin. Drug Deliv.; 2006; pp. 217-233; 3(2).

Moes, A.J.; "Gastroretentive Dosage Forms"; Critical Reviews in Therapeutic Drug Carrier Systems; 1993; pp. 143-195; 10(2).

Davis, Stanley, S.; "Formulation strategies for absorption windows"; DDT; Feb. 2005; pp. 249-257; vol. 10, No. 4.

Bardonnet et al.; "Gastroretentive dosage forms: Overview and special case of *Helicobacter pylori*"; Journal of Controlled Release; 2006; pp. 1-18; 111.

Foremost NF Flo Lactose, "A spray-dried mixture of crystalline and amorphous lactose", Foremost Farms USA, 1pg., Online Article

US 8,658,631 B1

Page 4

(56)

References Cited**OTHER PUBLICATIONS**

downloaded from the site: http://www.foremostfarms.com/Commercial/pdfs/Specifications/TDS_NF_Lactose_316.pdf, Document created on Jan. 28, 2010.

Freed et al. "pH control on nucleophilic/electrophilic oxidation", Int. J. Pharm., vol. 357, pp. 180-188 (2008).

International Search Report from related PCT Patent application No. PCT/US2009/036864 mailed Aug. 31, 2009, application now published as PCT Publication No. WO2009/114648 on Sep. 17, 2009.

Lab Basics Technical Library, Particle Size Conversion Table, Sigma-Aldrich, 3 pgs., Online Article downloaded from the site: <http://www.sigmaaldrich.com/chemistry/stockroom-reagents/learning-center/technical-library/particle-size-conversion.printerview.html> on Apr. 17, 2012.

Polyox Water-Soluble Resins, Technical Data, "Degradation of water-soluble resins", Form 326-00027-1002AMS (2002).

Polyox Water-Soluble Resins, Technical Data, "Water-soluble resin storage stability", Form 326-00044-0704MAB (2004).

Waterman et al., "Stabilization of pharmaceuticals to oxidative degradation", Pharm. Dev. Tech., vol. 7, No. 1, pp. 1-32 (2002).

Zhang et al., "Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release", Pharm. Dev. Tech., vol. 6, No. 2, pp. 131-144 (2001).

Meert et al., A preclinical comparison between different opioids: antinociceptive versus adverse effects; Pharmacology, Biochemistry & Behavior; 80(2):309-26, Feb. 2005.

Doteuchi et al., "Pharmacological Studies of Oxycodone Hydrochloride 1. Antinociceptive Effect and General Pharmacology"; Oyo Yakuri. 49(3); 1995; 257-273.

Miller et al., "Physical and chemical characteristics of some high purity magnesium stearate and palmitate powders"; Intl Journal of Pharmaceutics, 23 (1985), 55-67.

Kim, Chong-Ju, "Effects of Drug Solubility, Drug Loading, and Polymer Molecular Weight on Drug Release from Polyox Tablets", Drug Development and Industrial Pharmacy; 24(7), (1998), 645-651.

Waterman, Kenneth, C., "A Critical Review of Gastric Retentive Controlled Drug Delivery", Pharmaceutical Development and Technology, 12:1-10, (2007).

Arora et al., "Floating Drug Delivery Systems: A Review", AAPS PharmSciTech (2005), 6(3) Article 47 E372-390.

Klausner et al., "Novel Gastroretentive Dosage Forms: Evaluation of Gastroretentivity and Its Effect on Levodopa Absorption in Humans"; Pharmaceutical Research, Vol. 20, No. 9, Sep. 2003; pp. 1466-1473.

Klausner, et al., "Novel levodopa gastroretentive dosage form: in-vivo evaluation in dogs", Journal of Controlled Release 88 (2003) 117-126.

* cited by examiner

U.S. Patent

Feb. 25, 2014

Sheet 1 of 49

US 8,658,631 B1

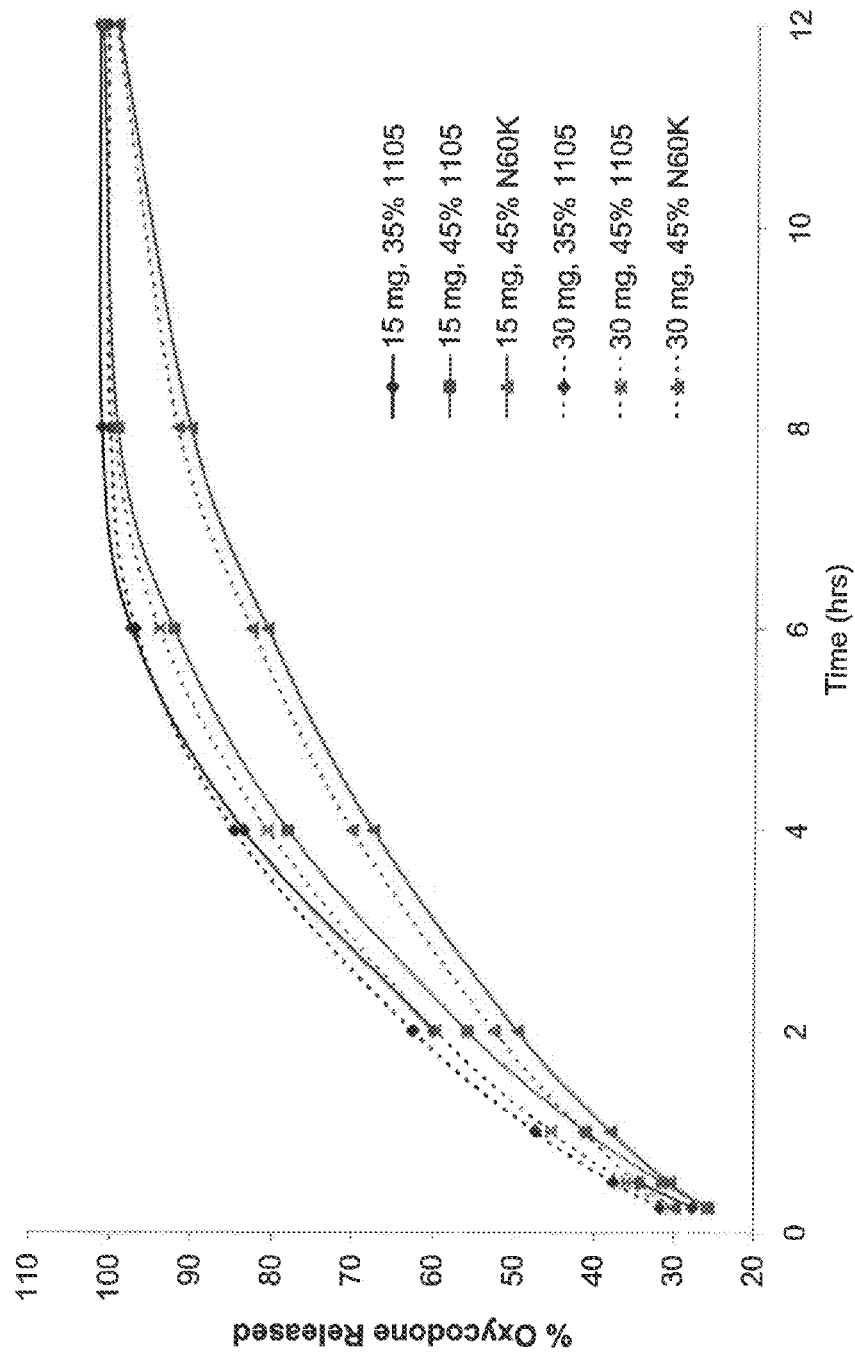


FIG. 1

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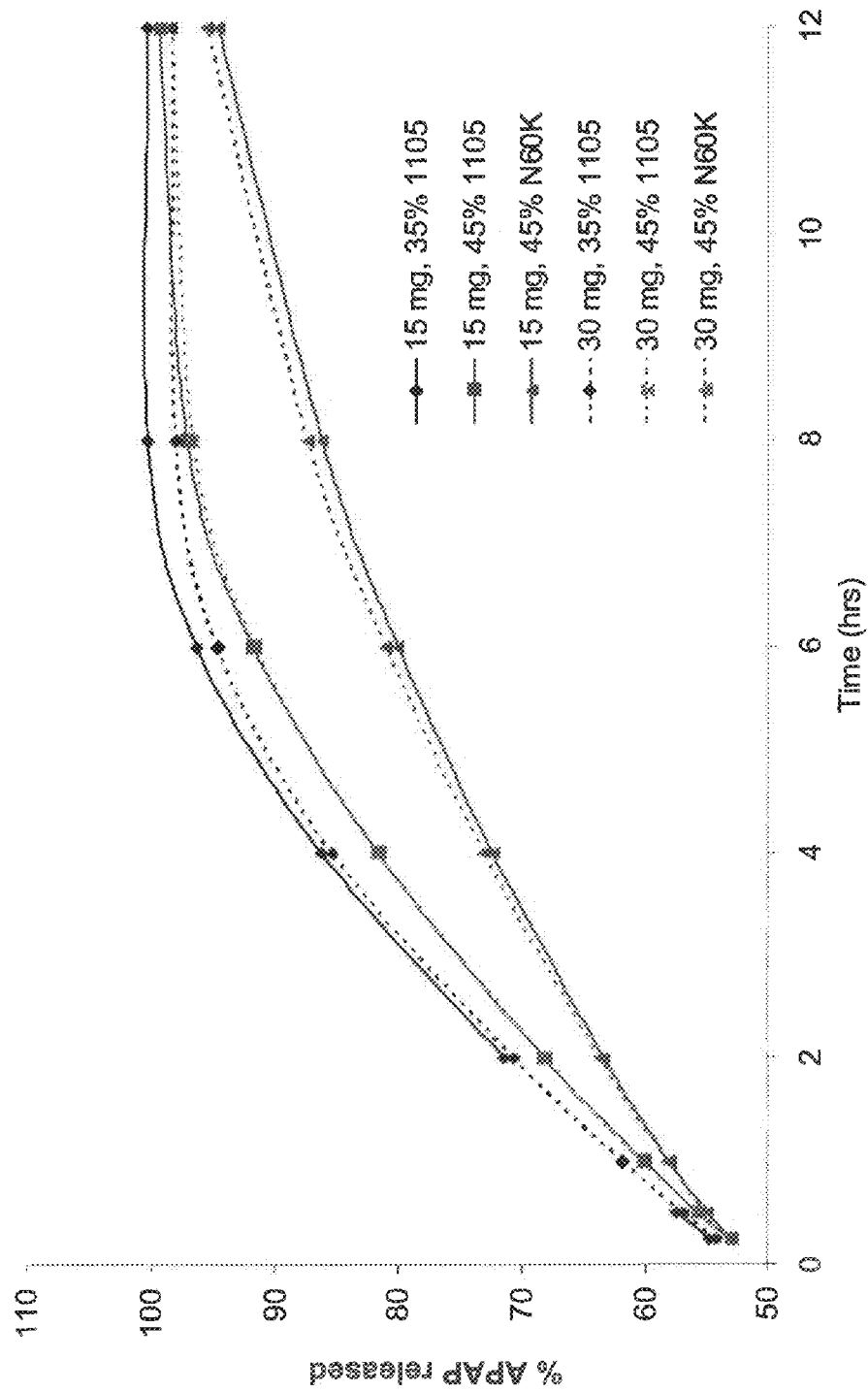


FIG. 2

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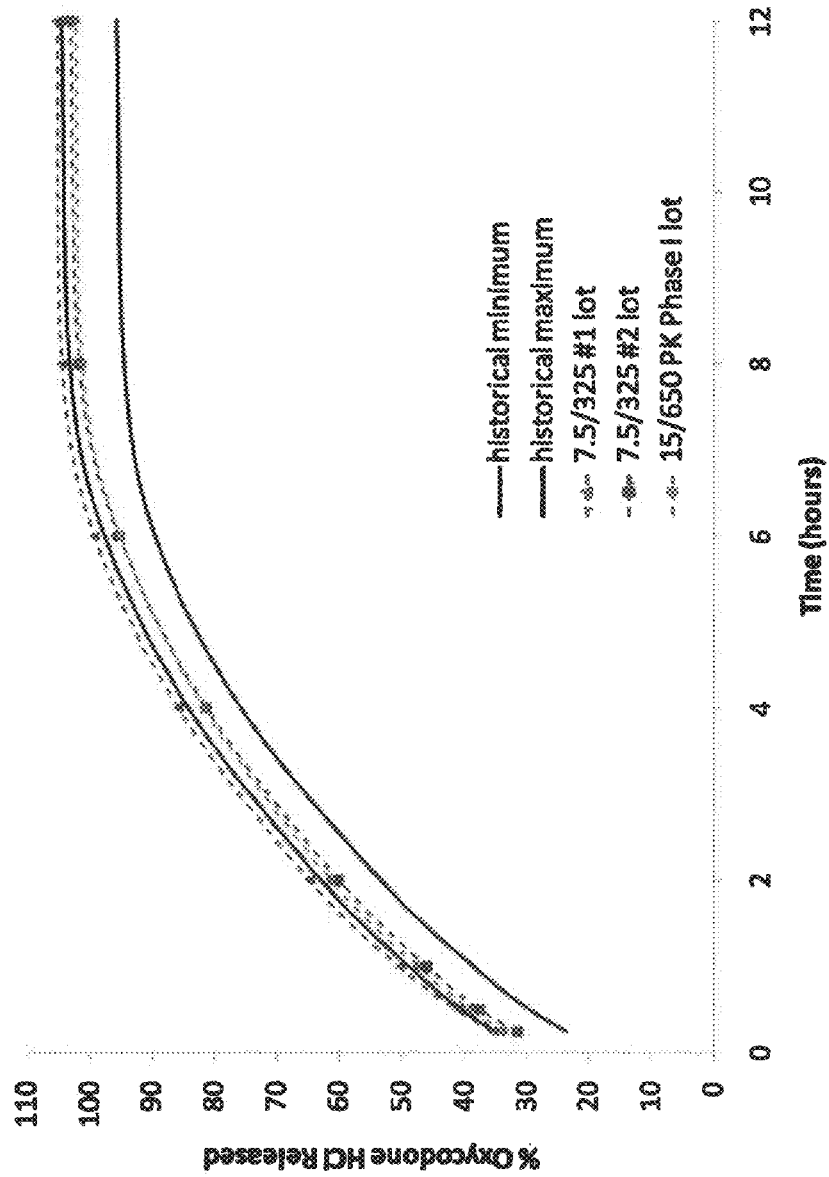


FIG. 3

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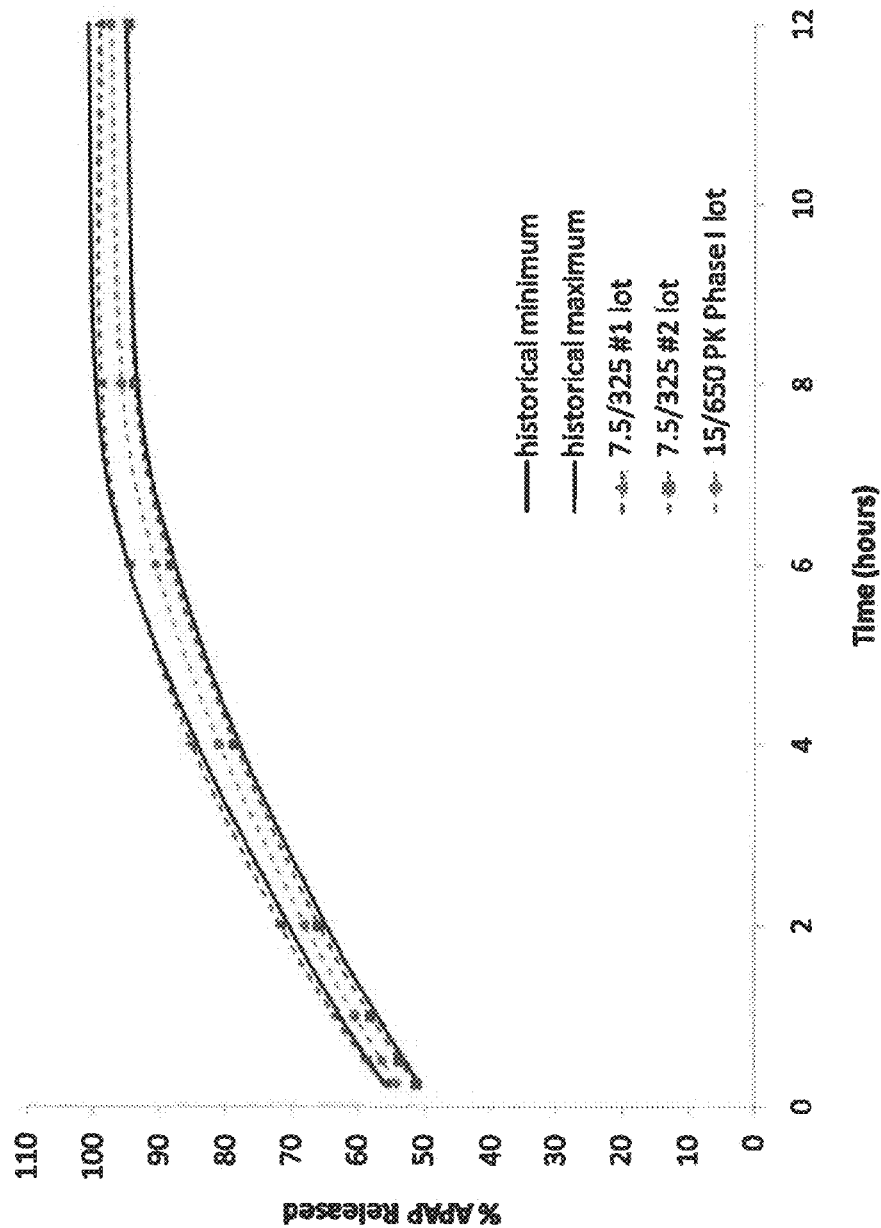


FIG. 4

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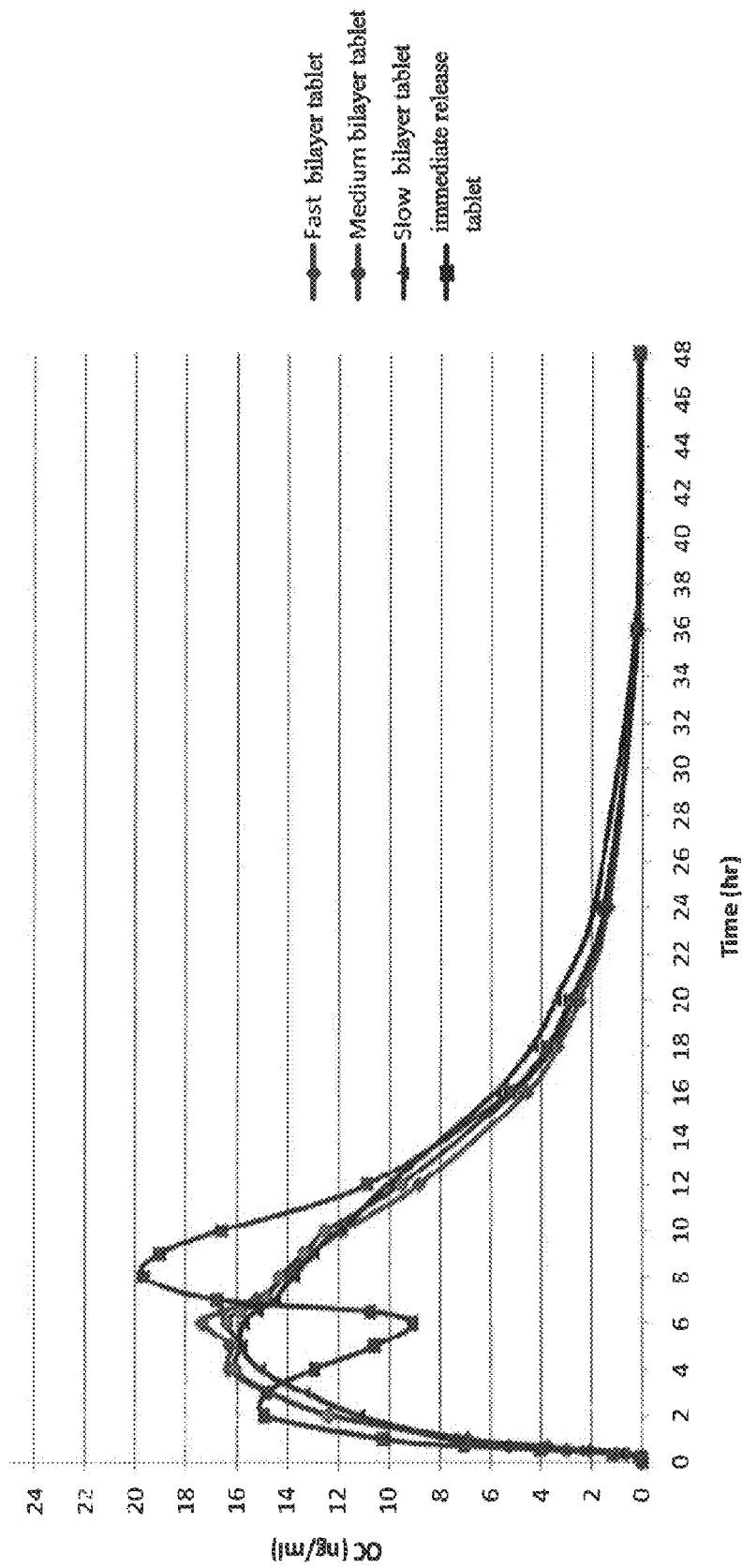


FIG. 5

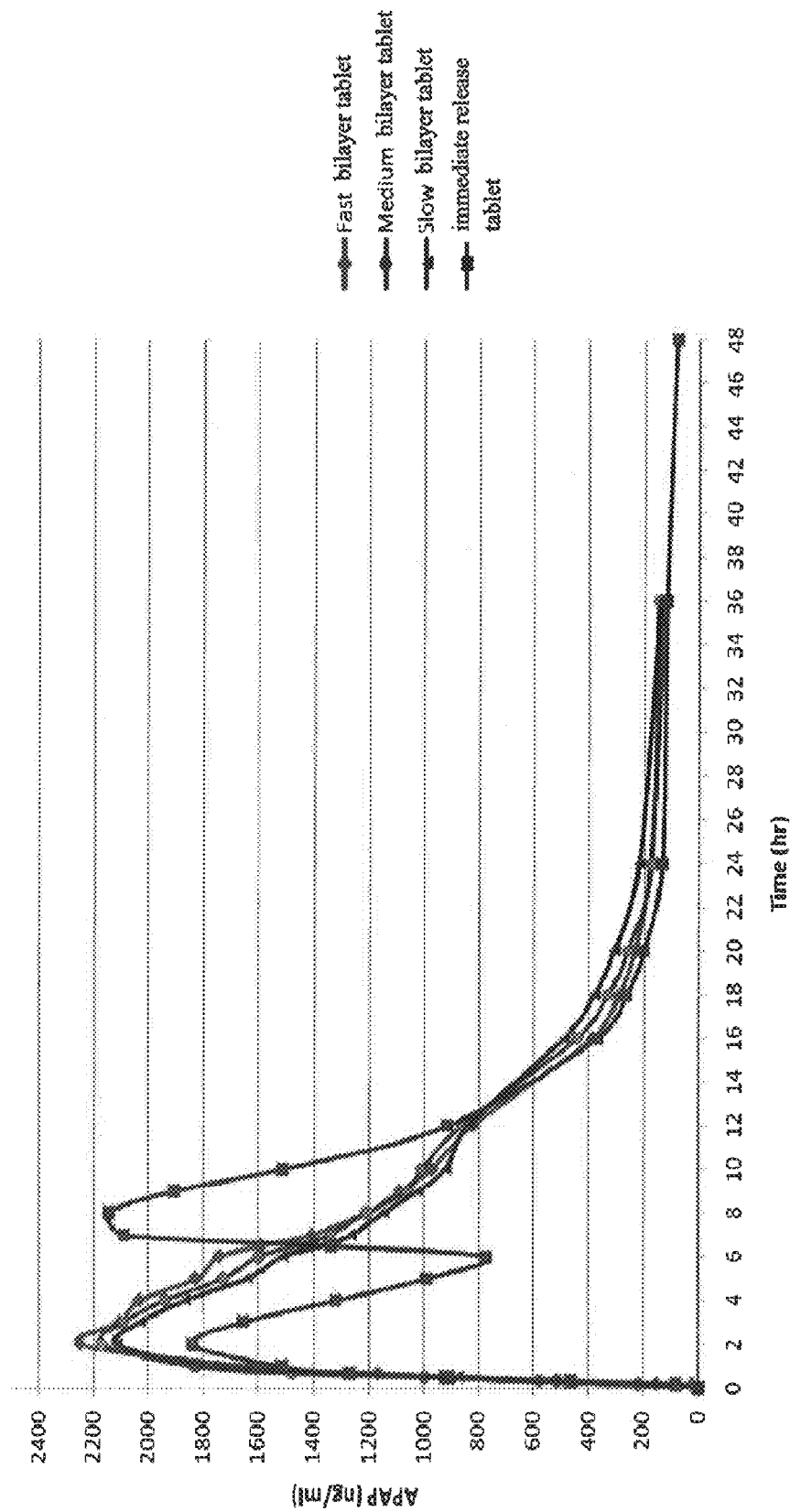


FIG. 6

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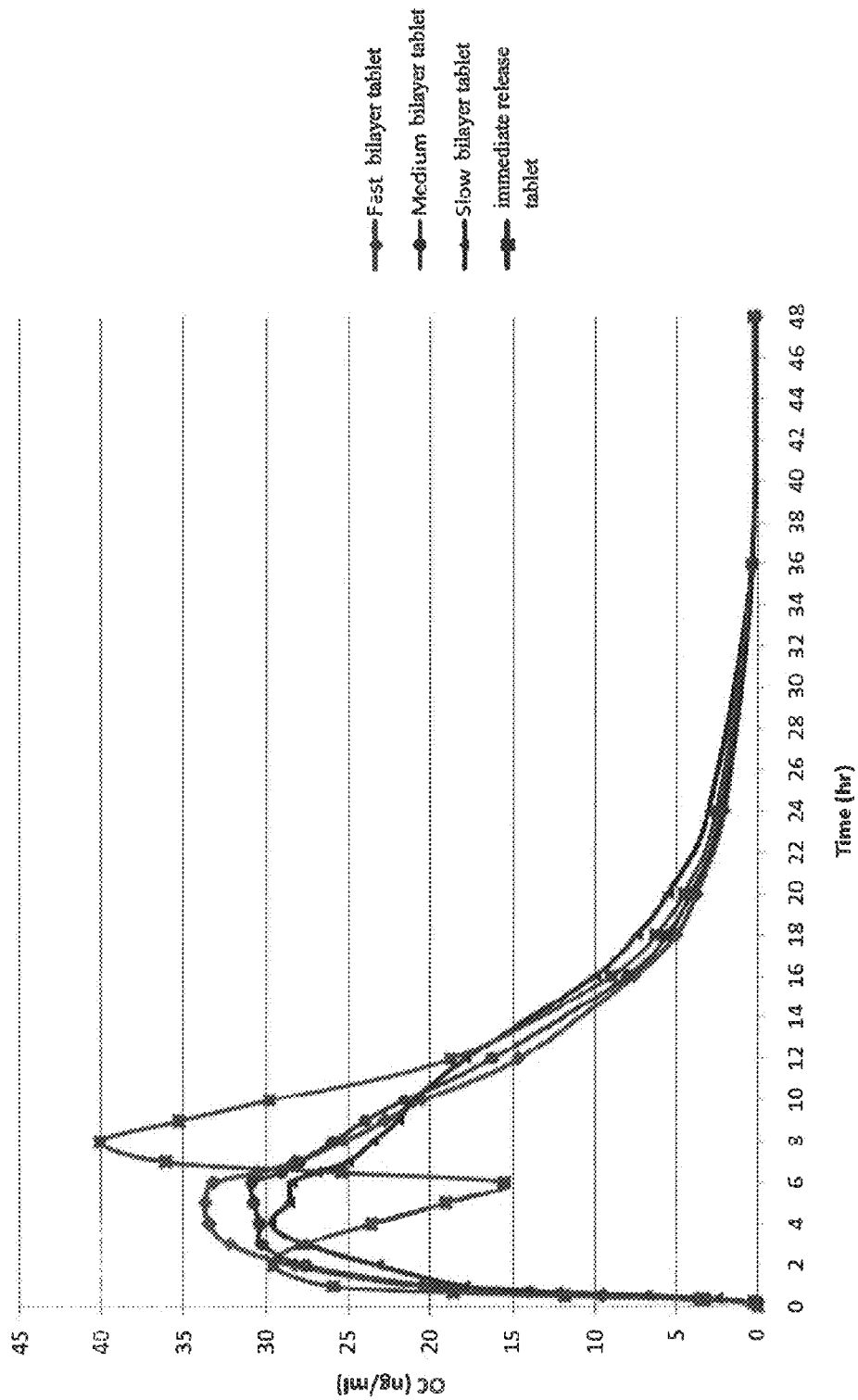


FIG. 7

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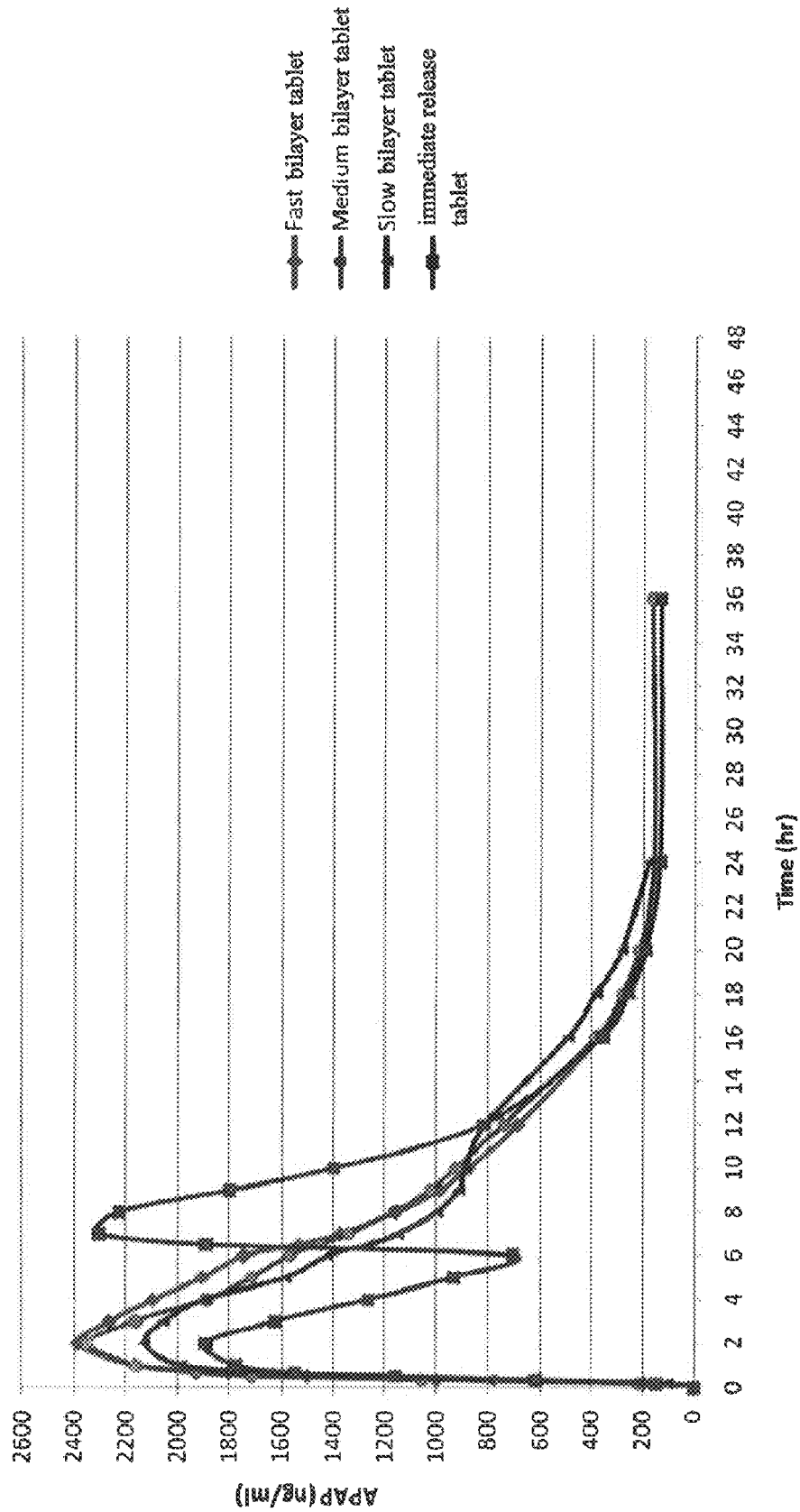


FIG. 8

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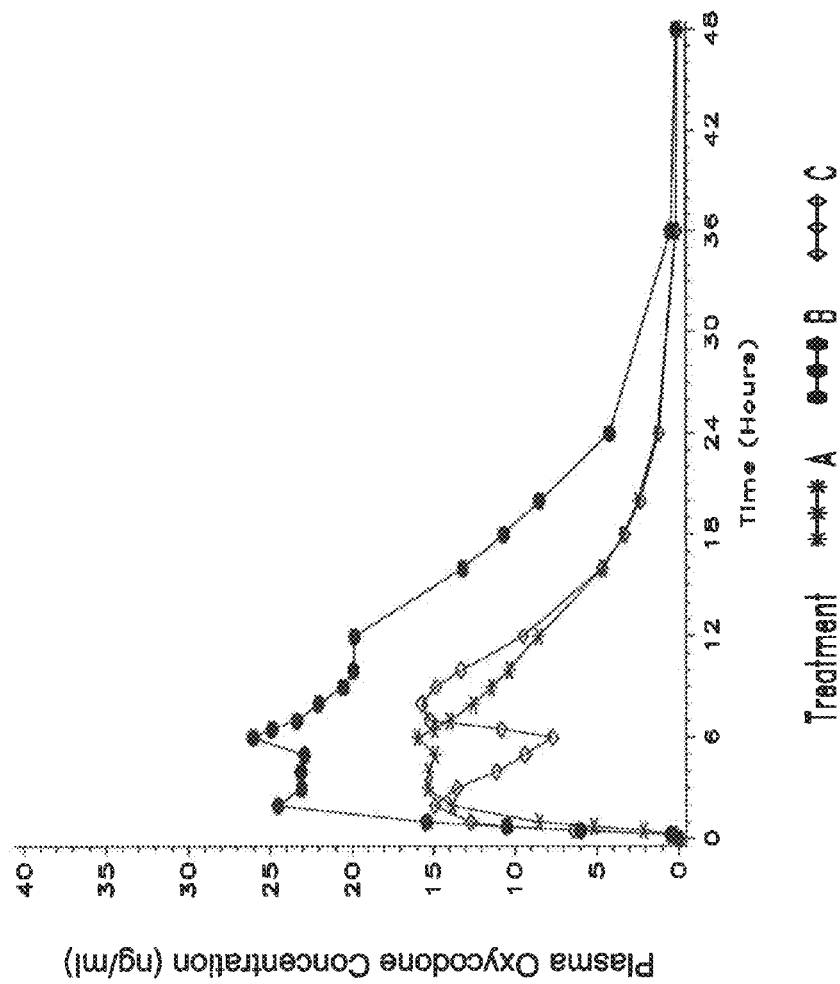


FIG. 9

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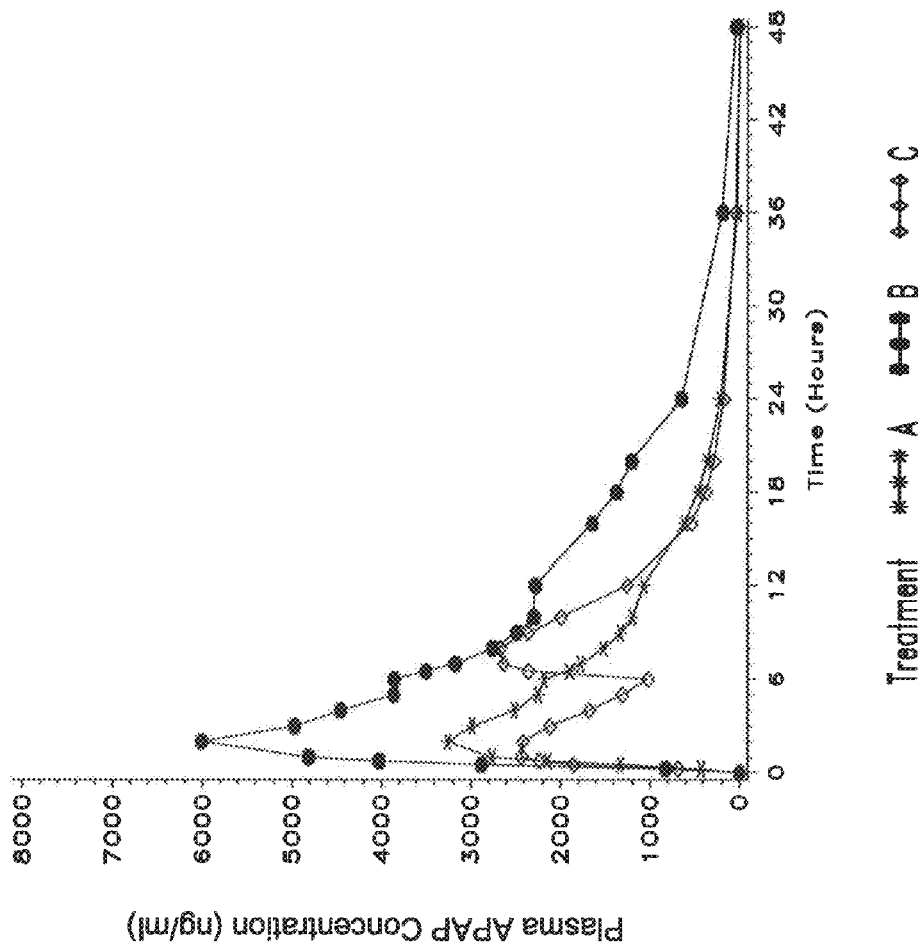


FIG. 10

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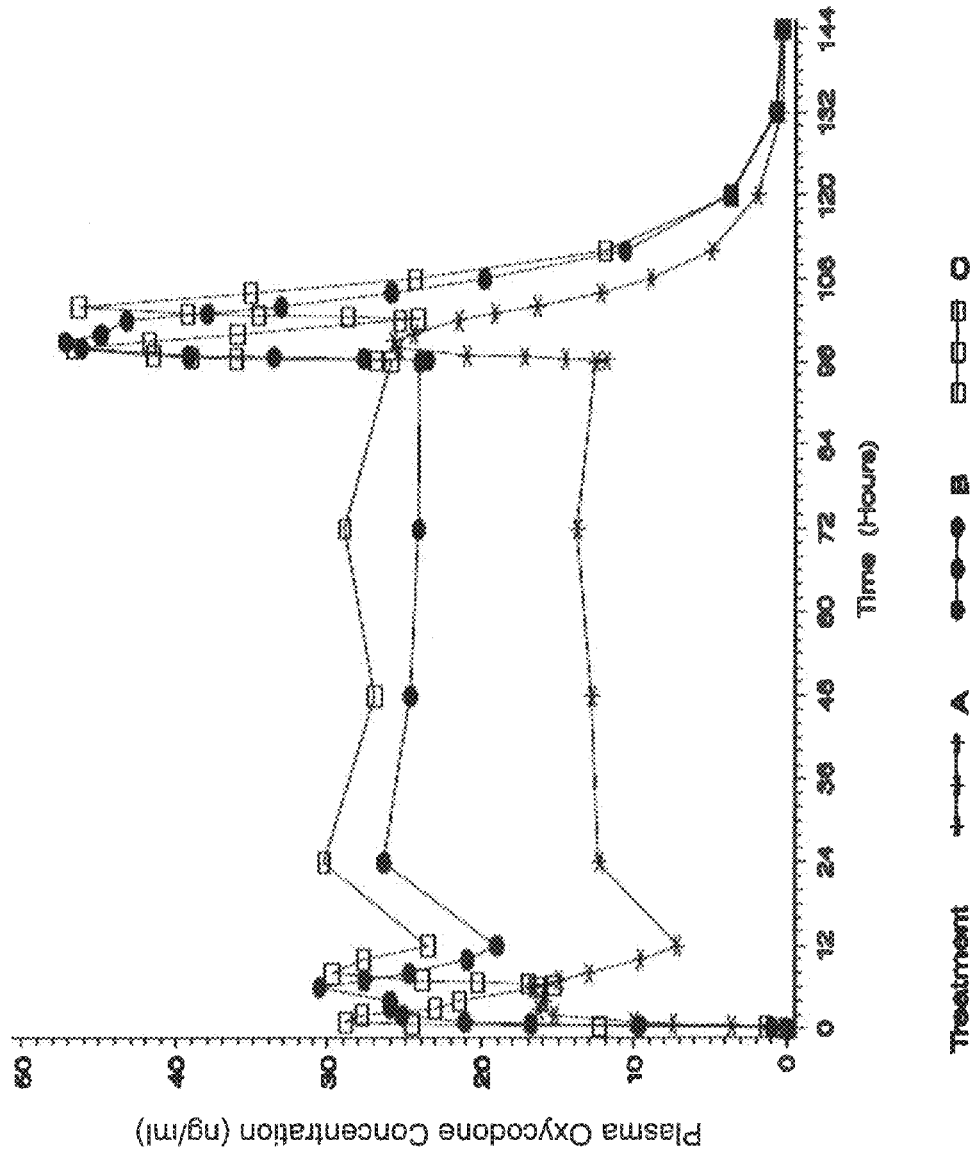


FIG. 11

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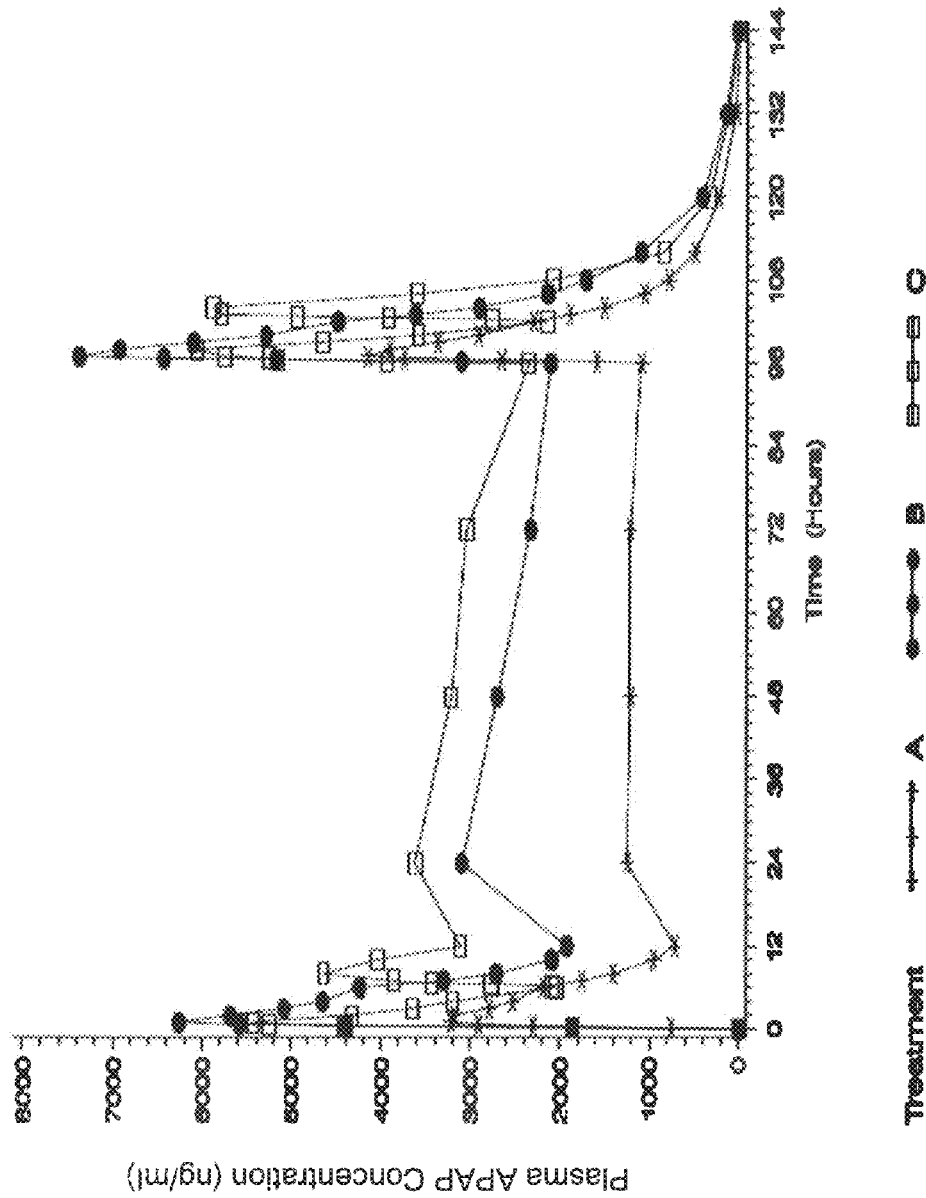


FIG. 12

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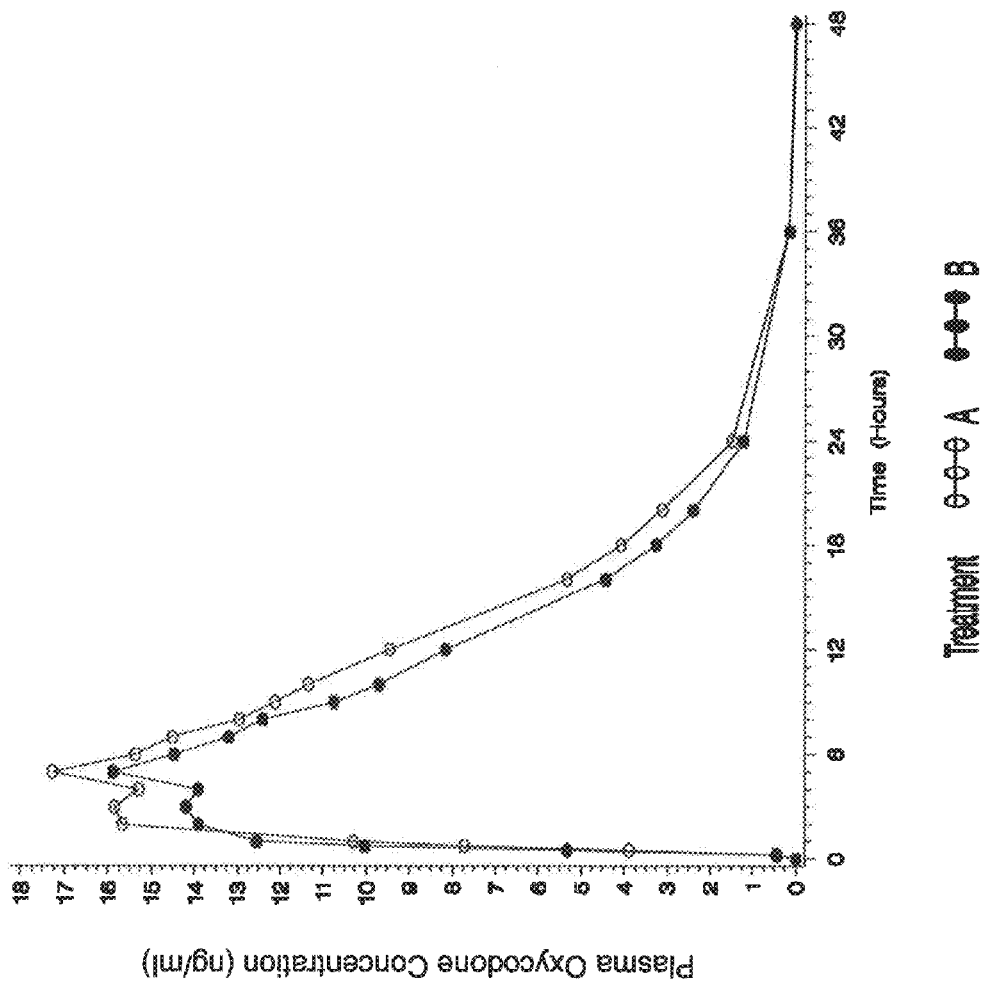


FIG. 13

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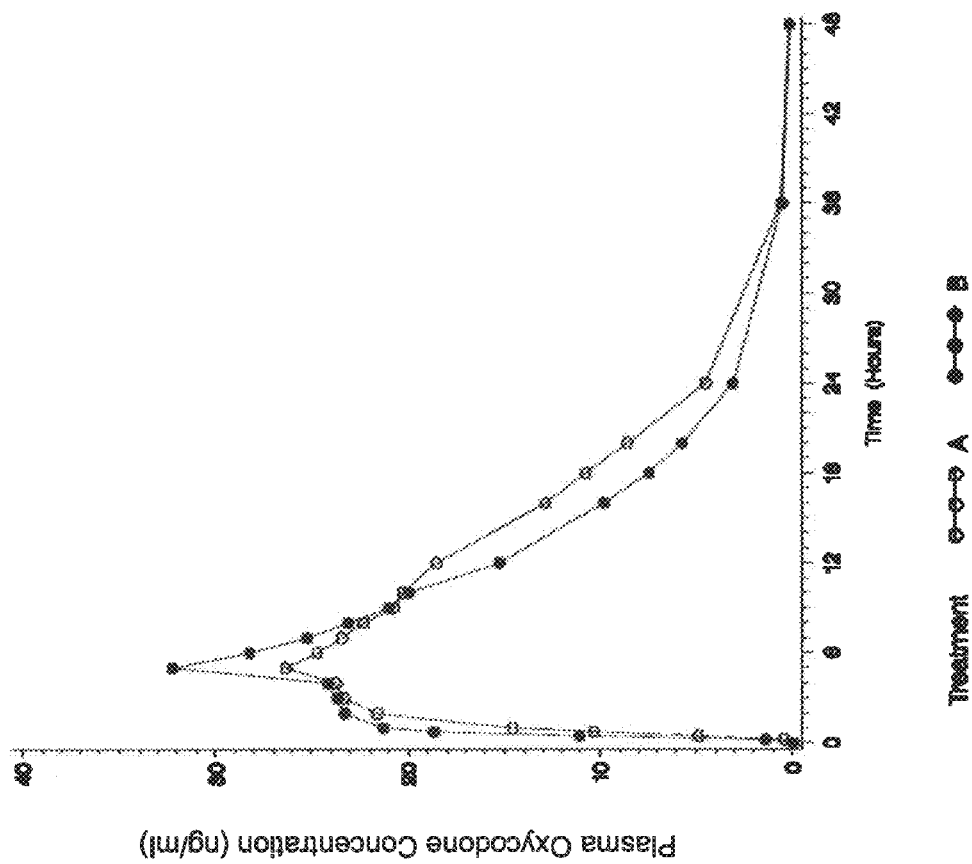


FIG. 14

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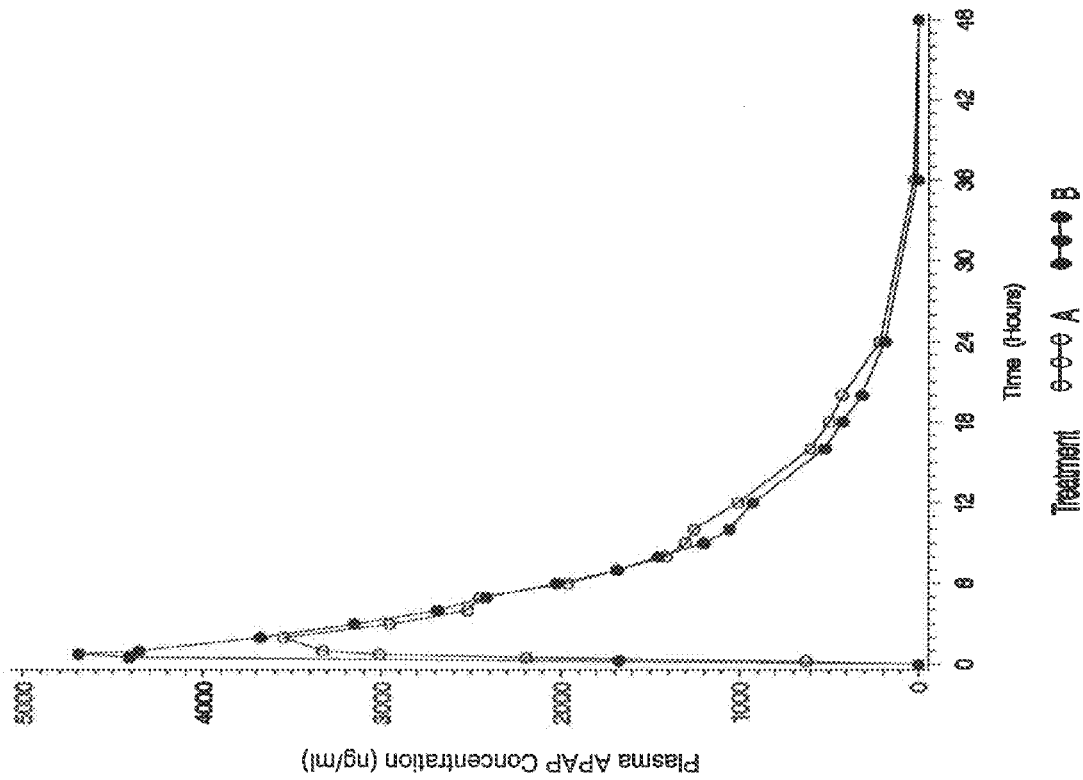


FIG. 15

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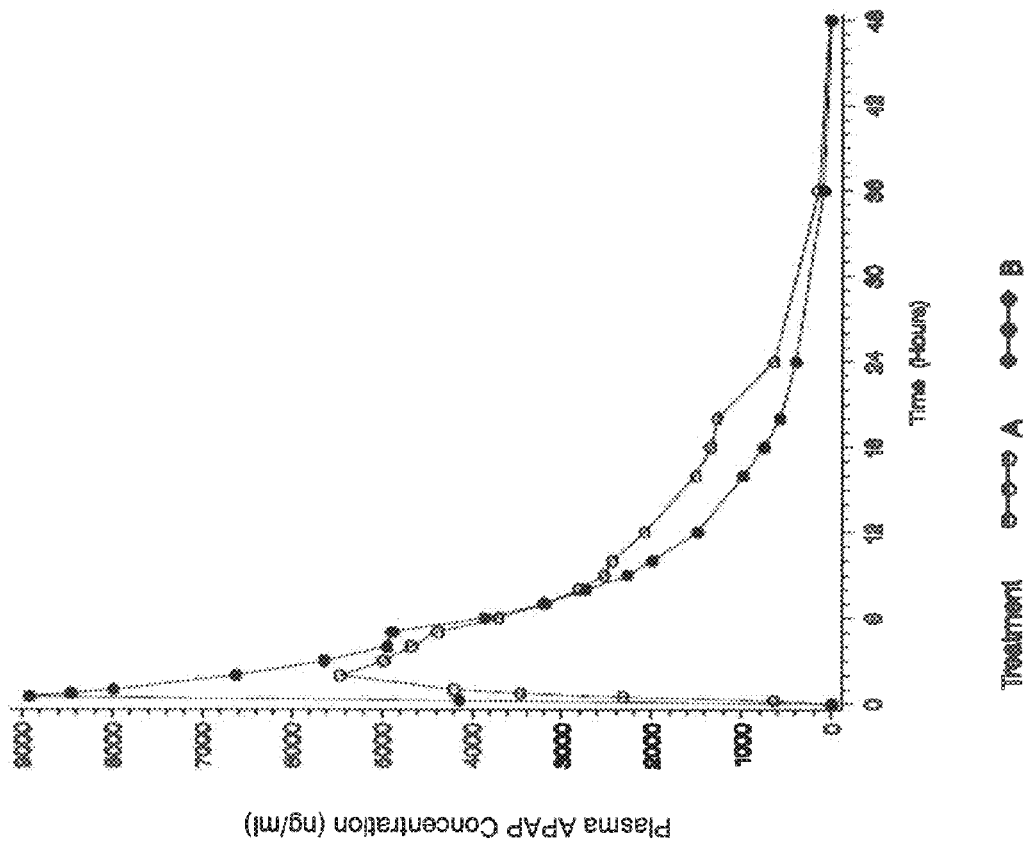


FIG. 16

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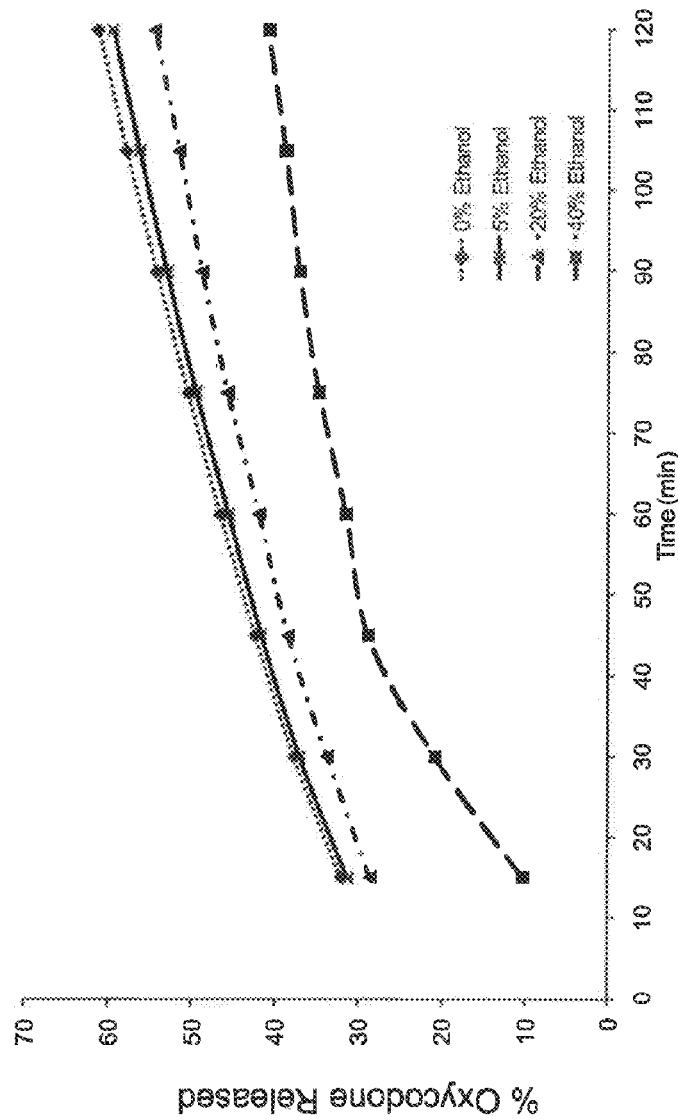


FIG. 17

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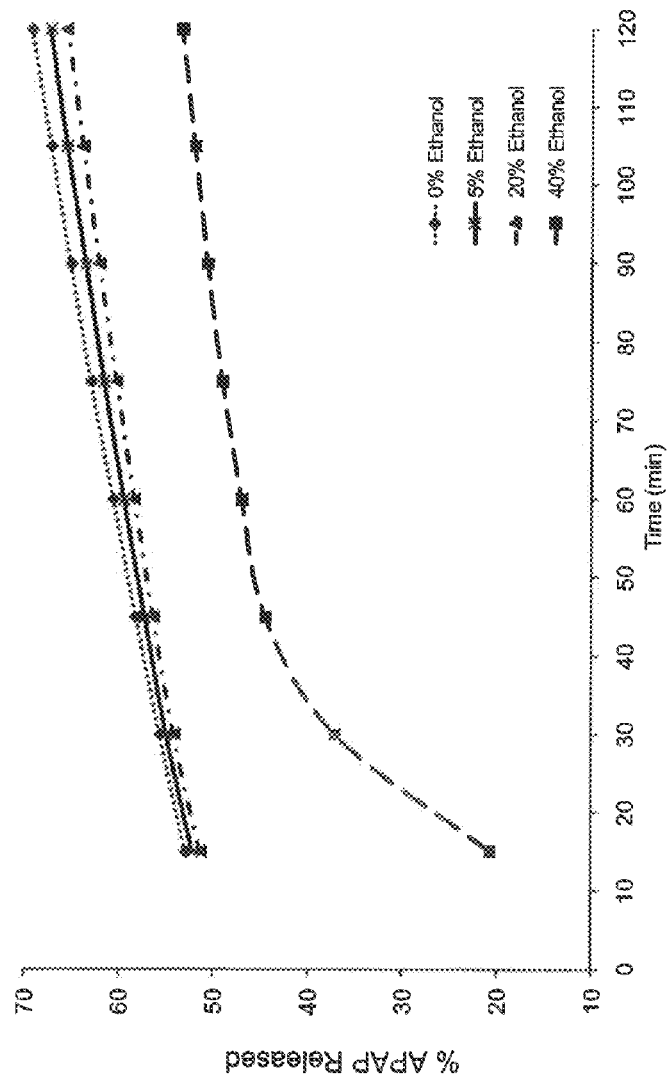


FIG. 18

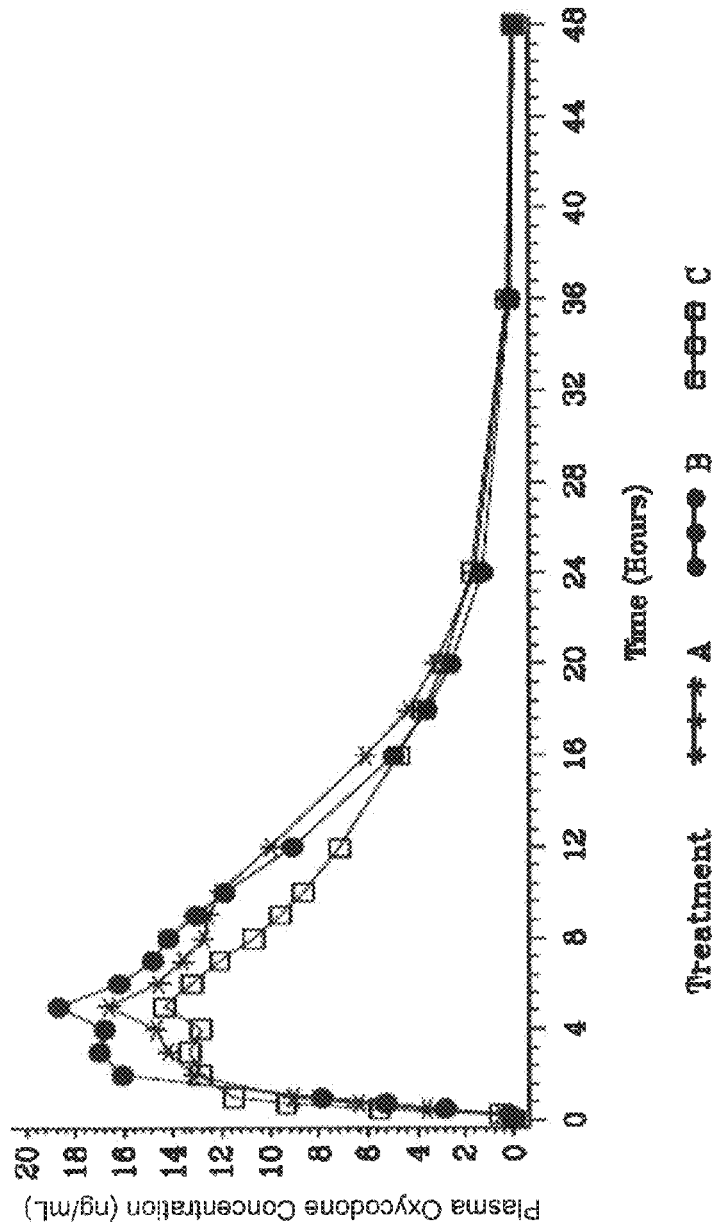


FIG. 19

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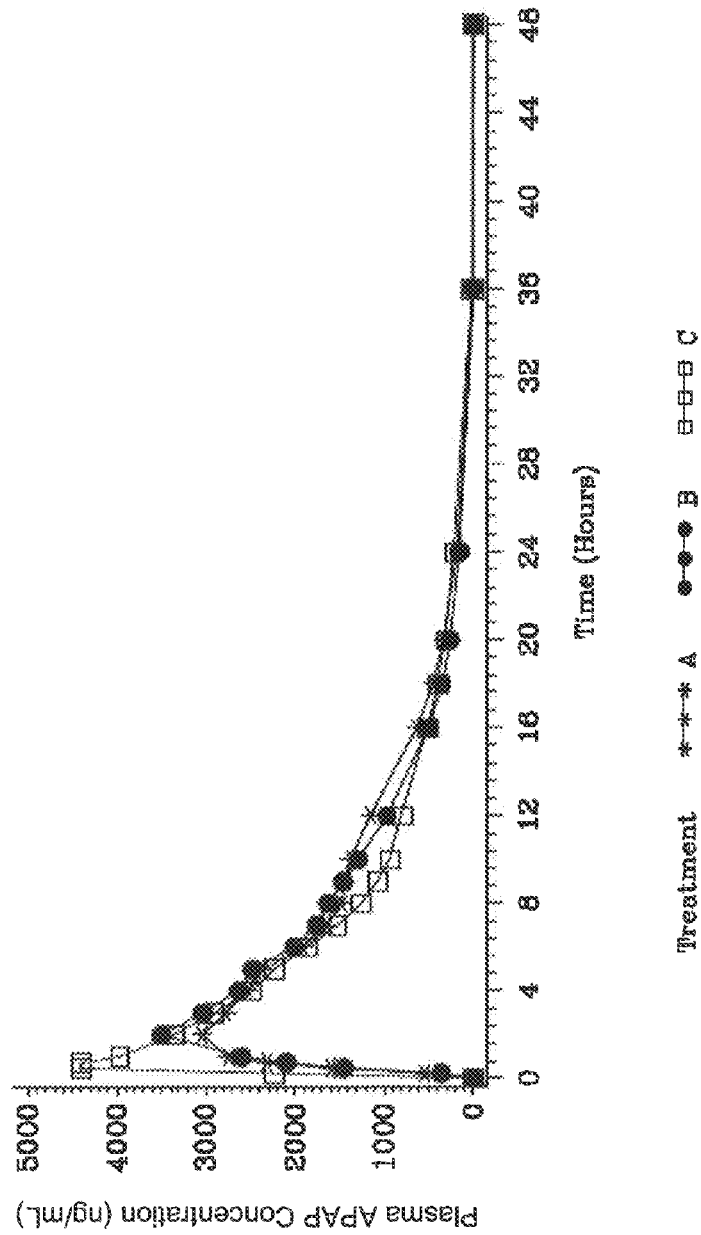


FIG. 20

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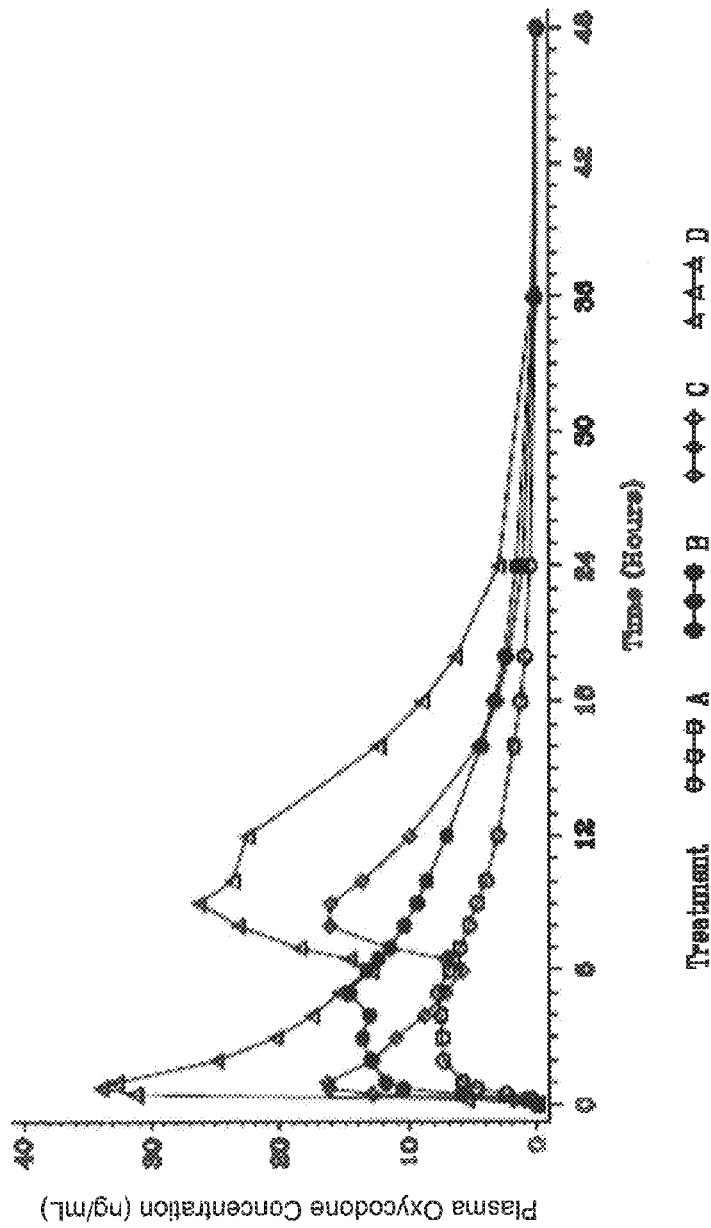


FIG. 21

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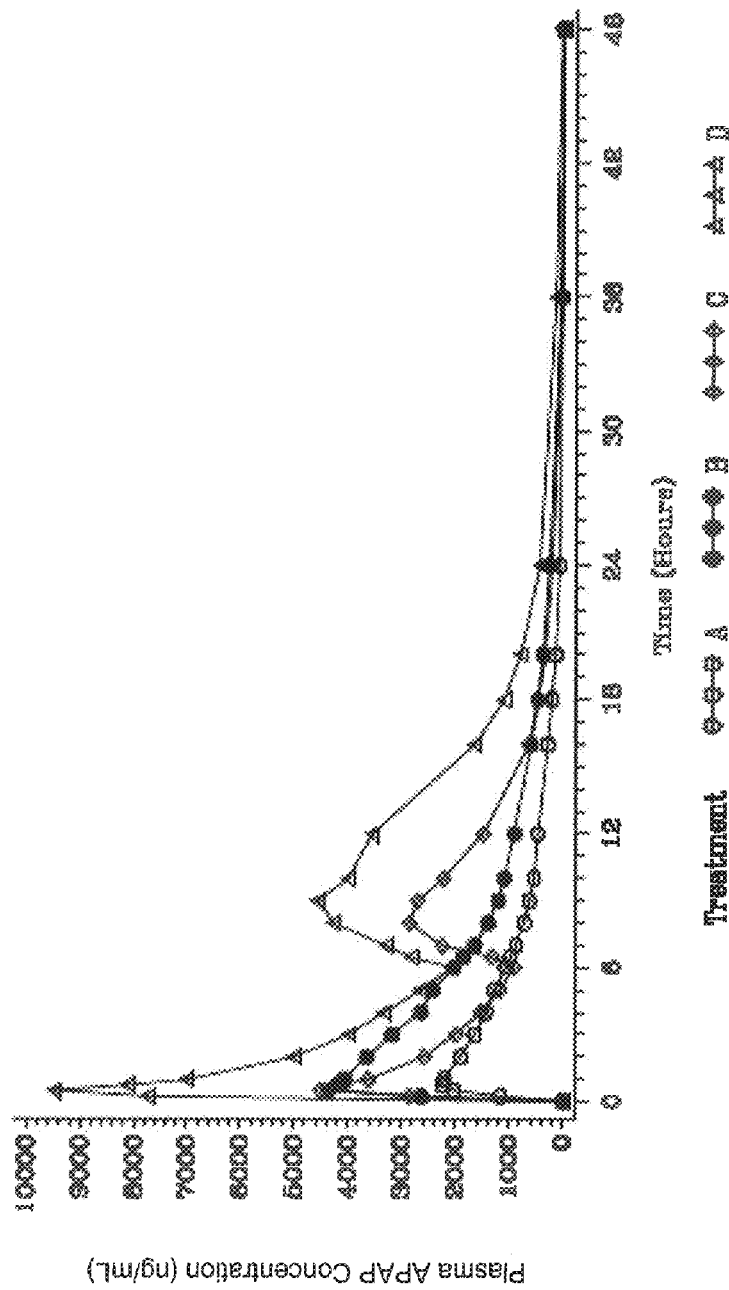


FIG. 22

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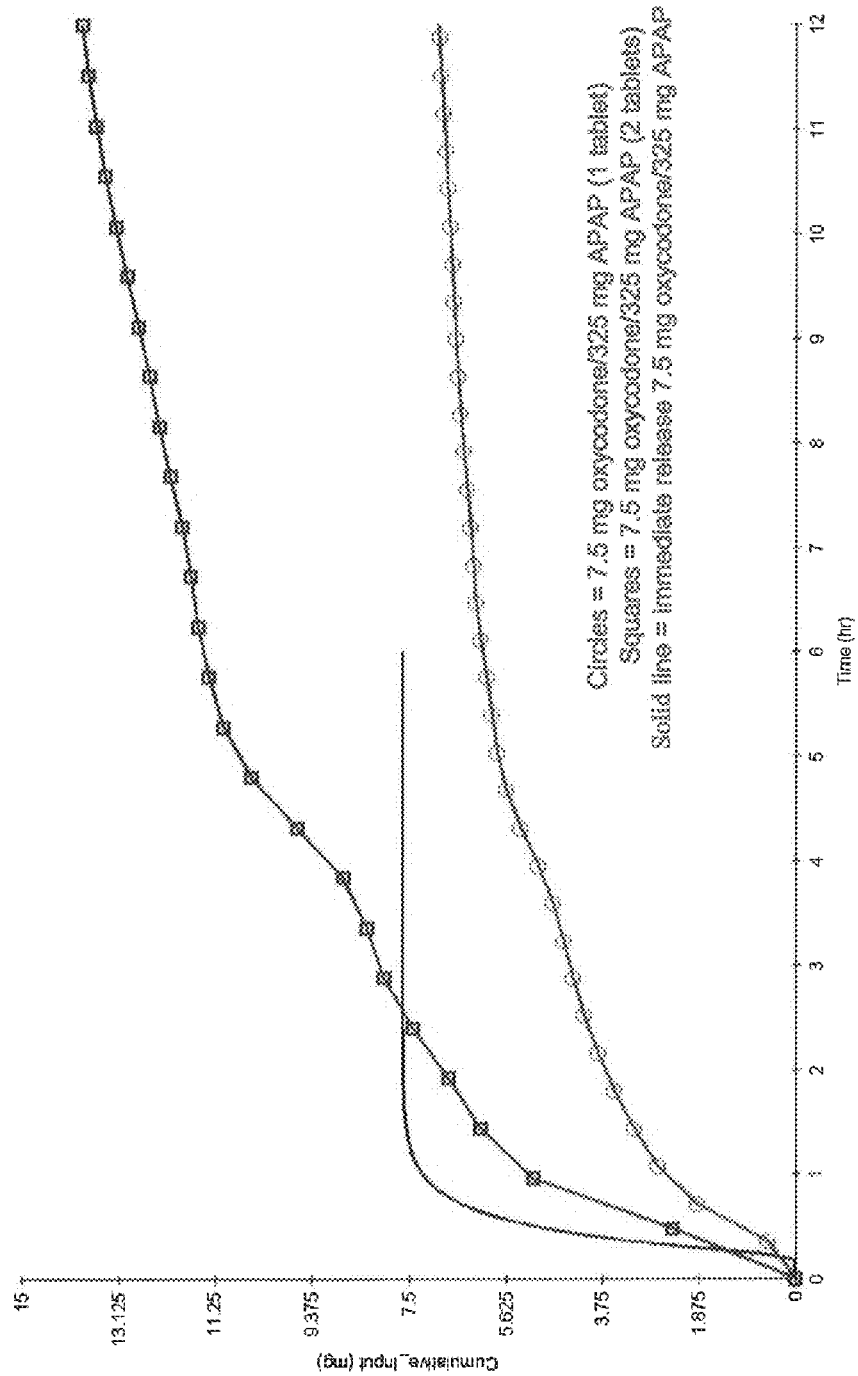


FIG. 23

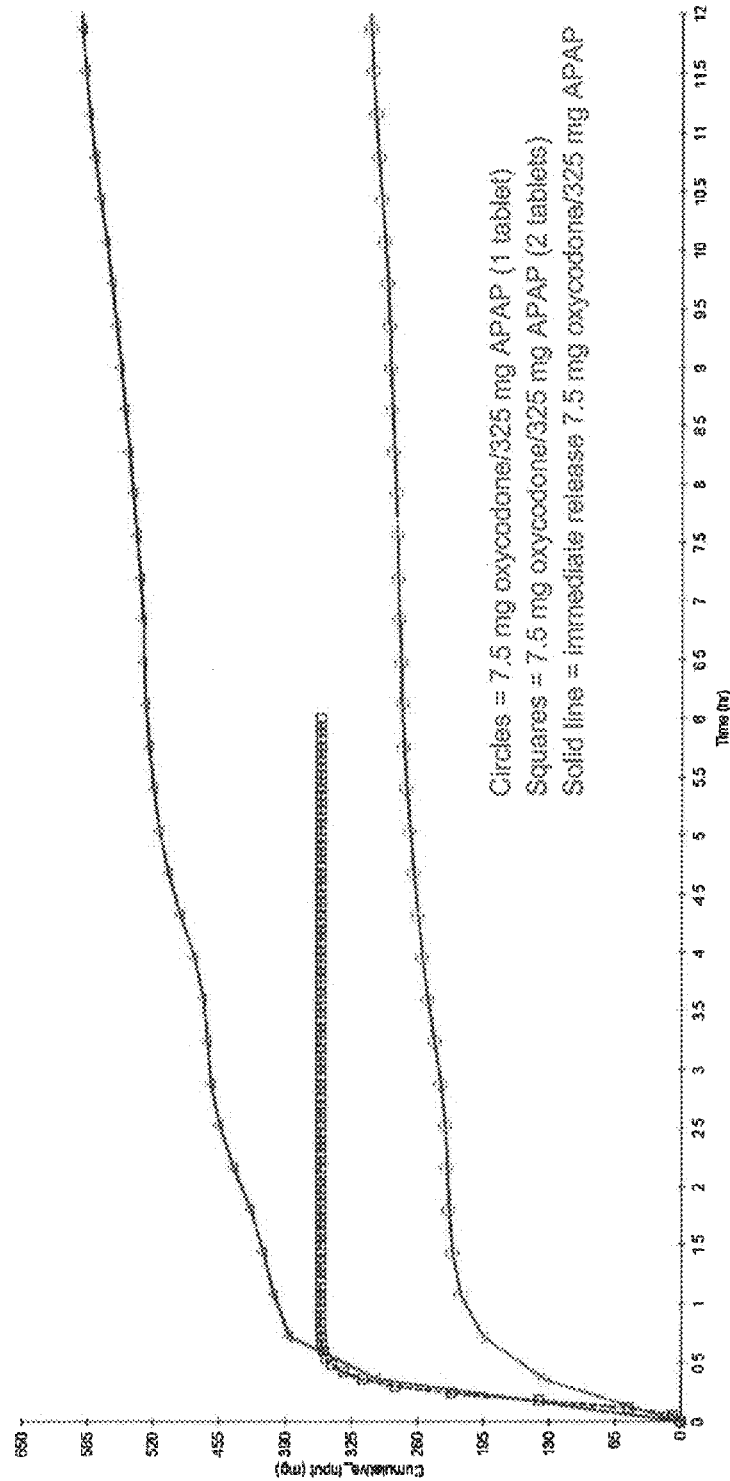


FIG. 24

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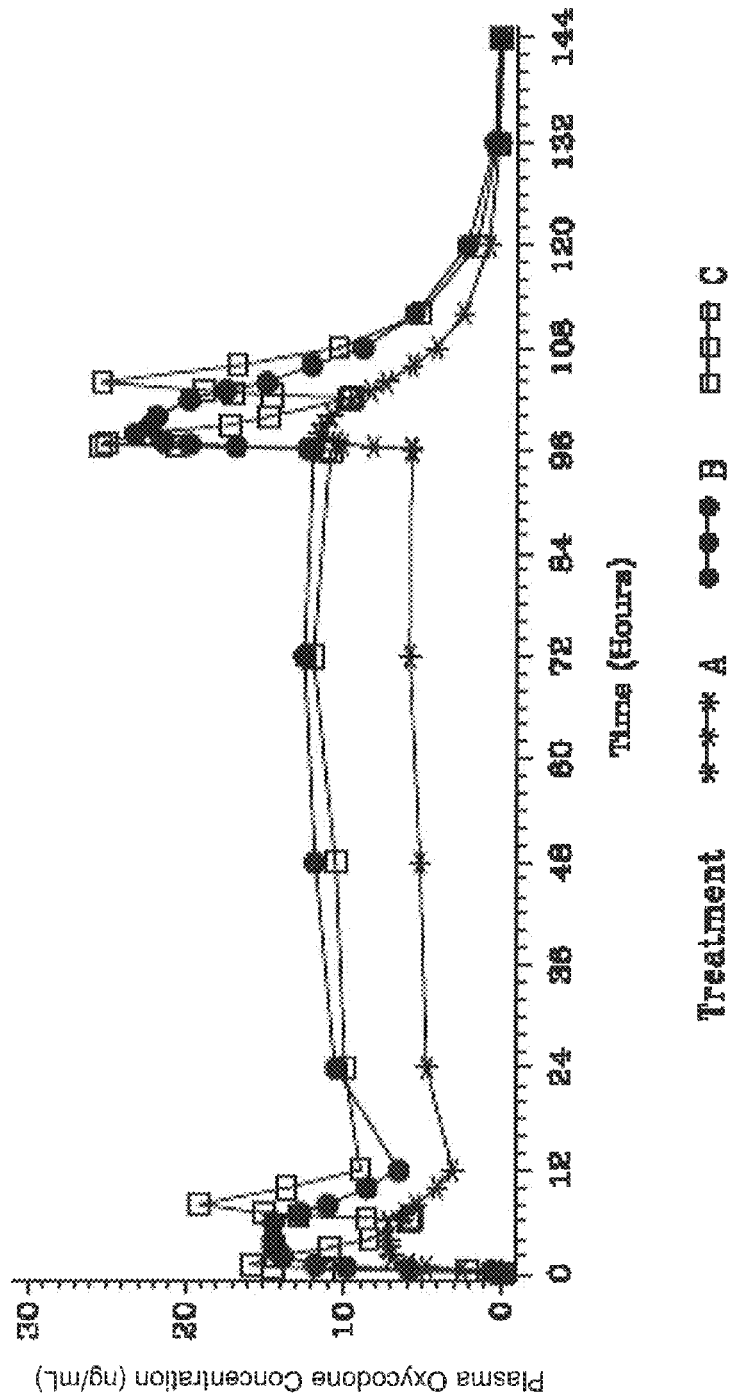


FIG. 25

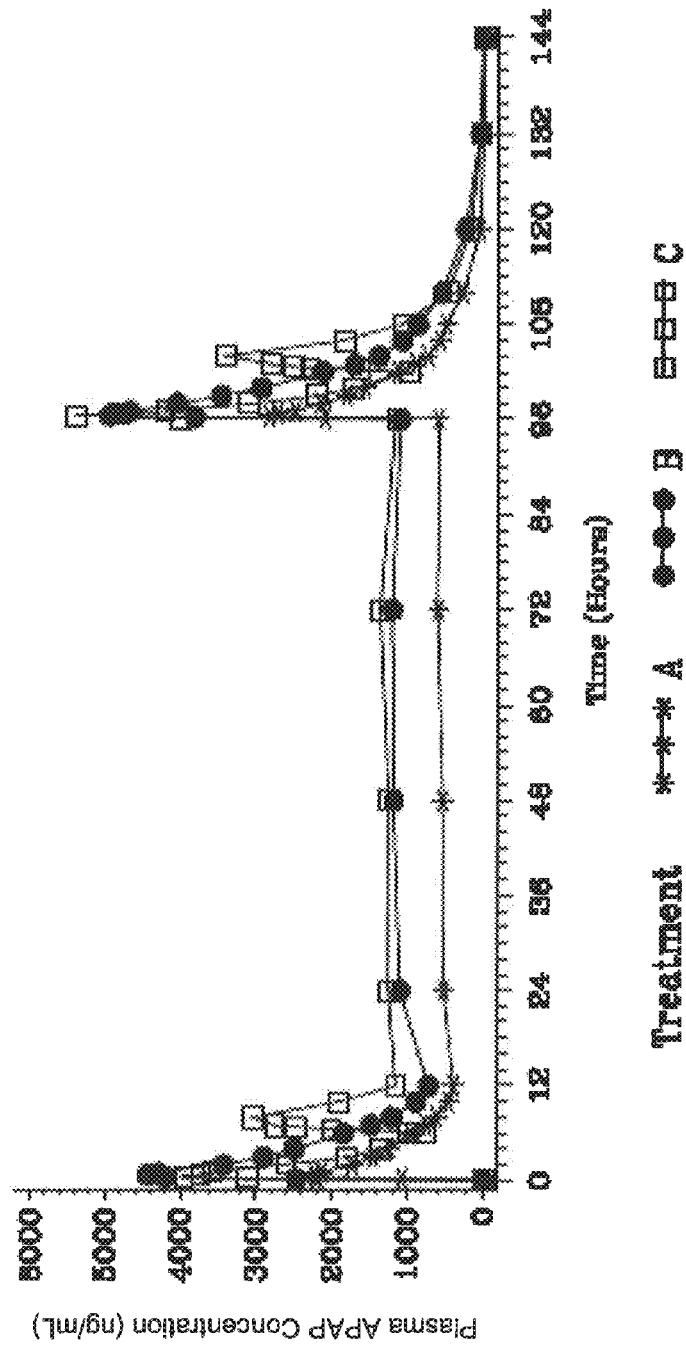


FIG. 26

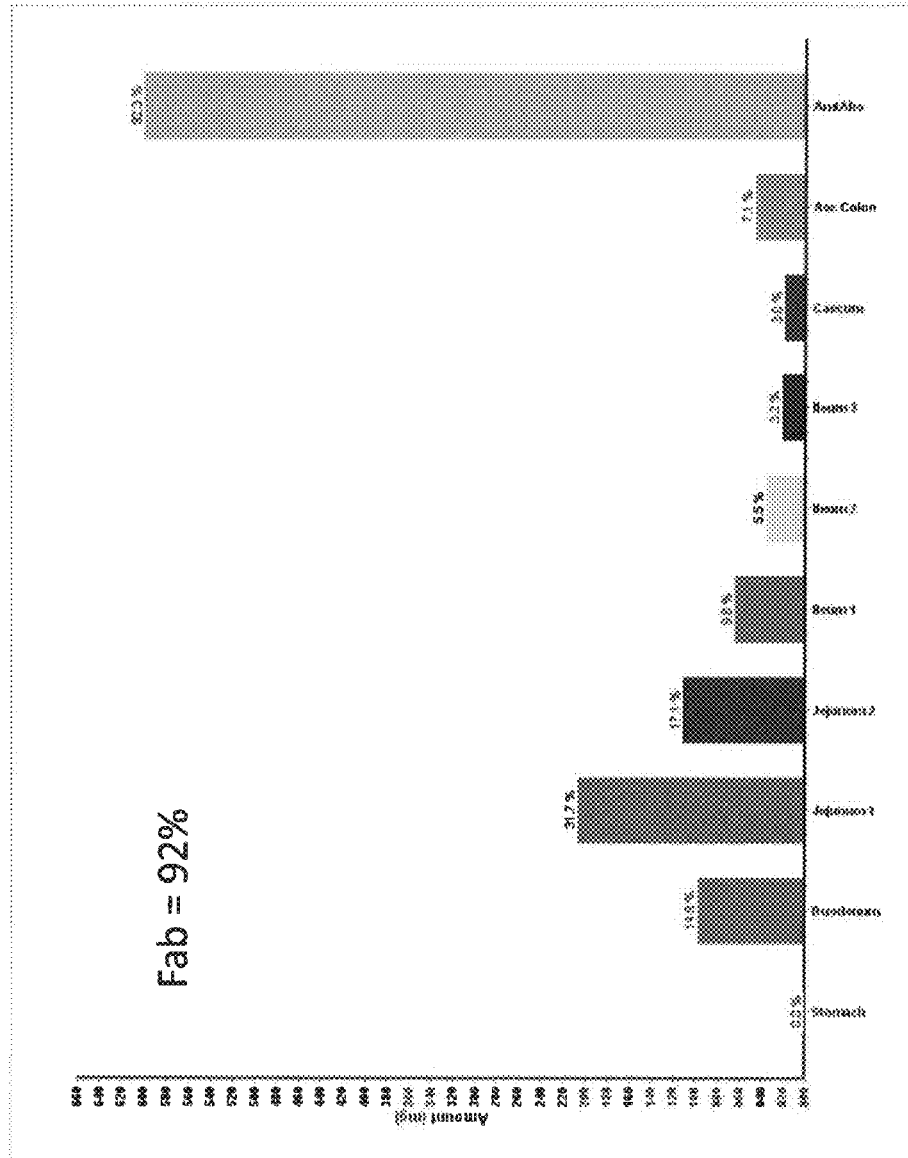
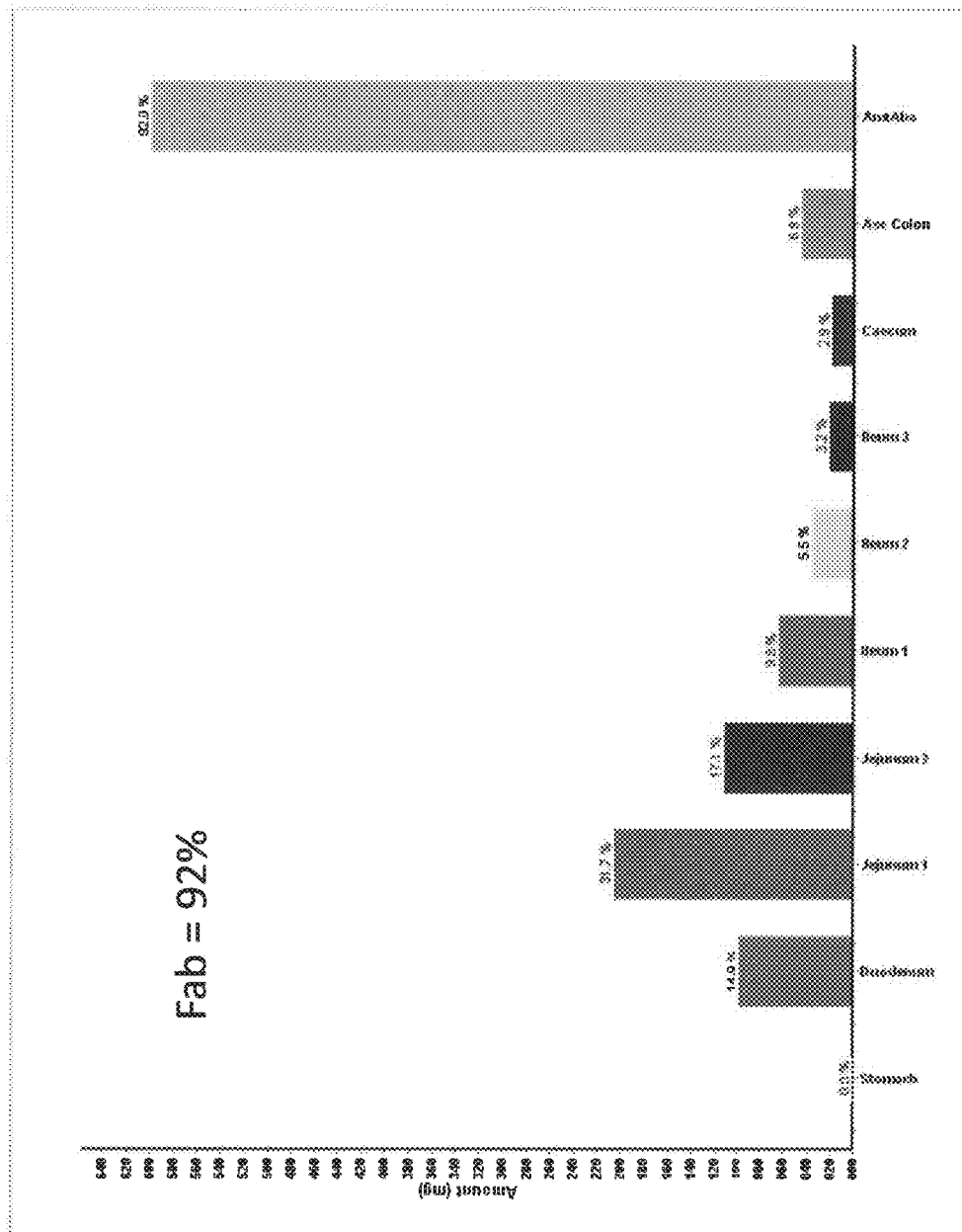
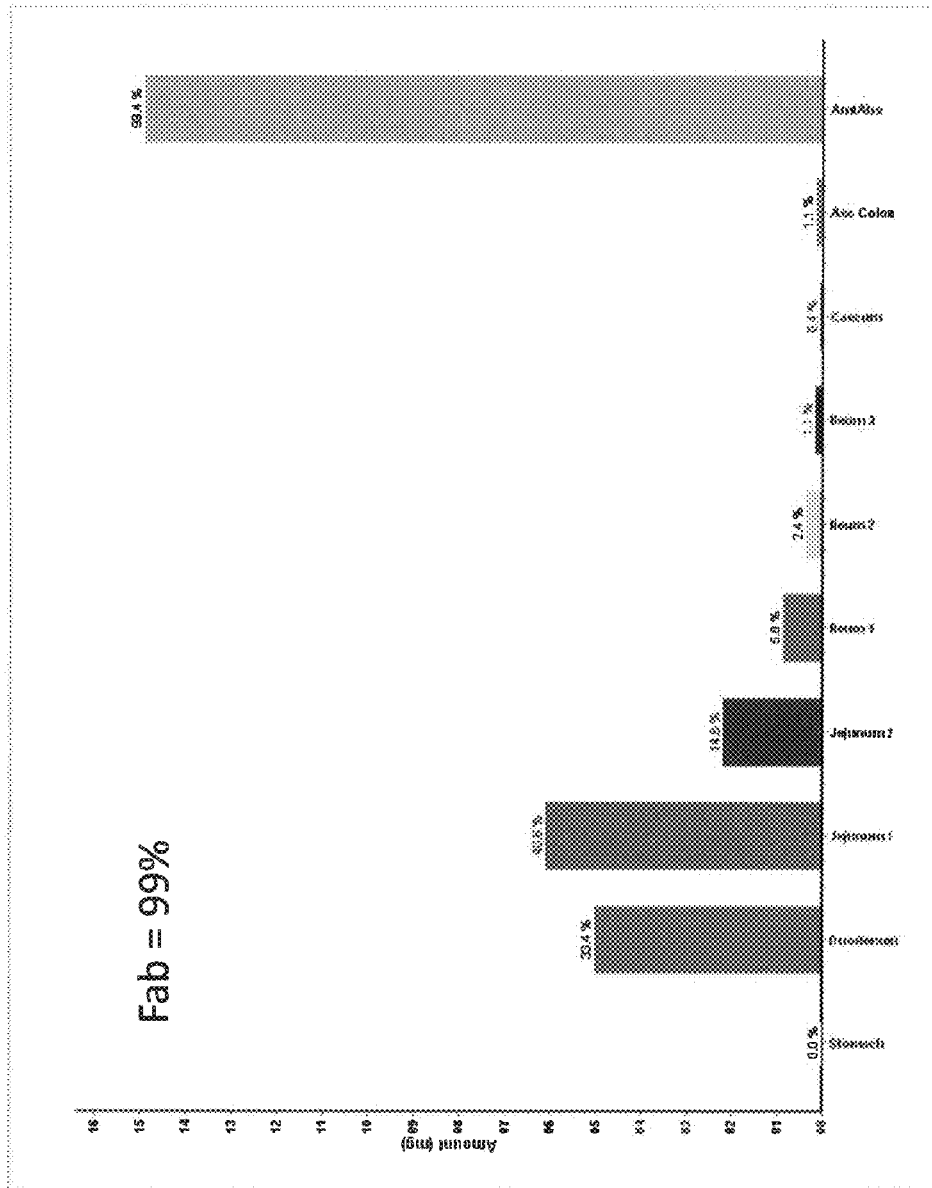
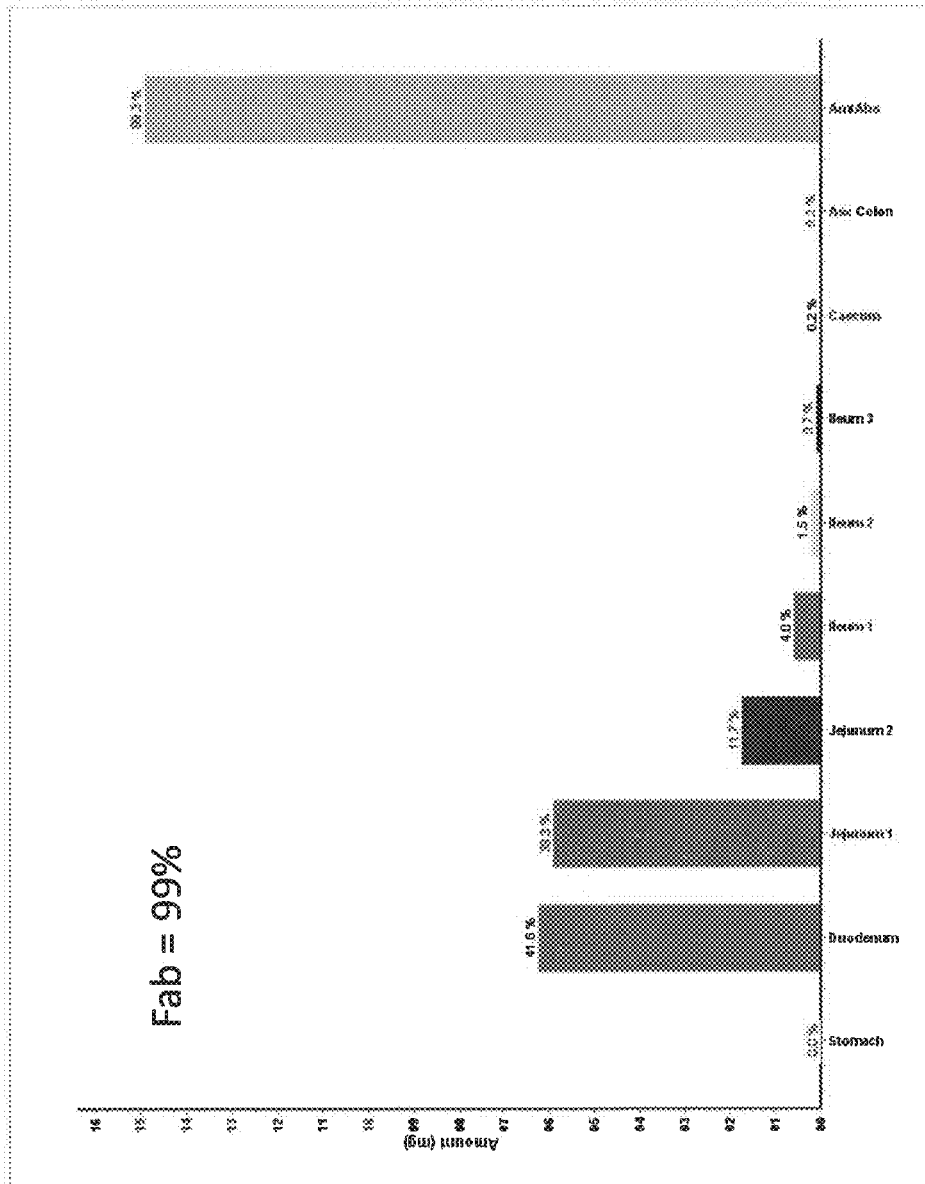


FIG. 27A







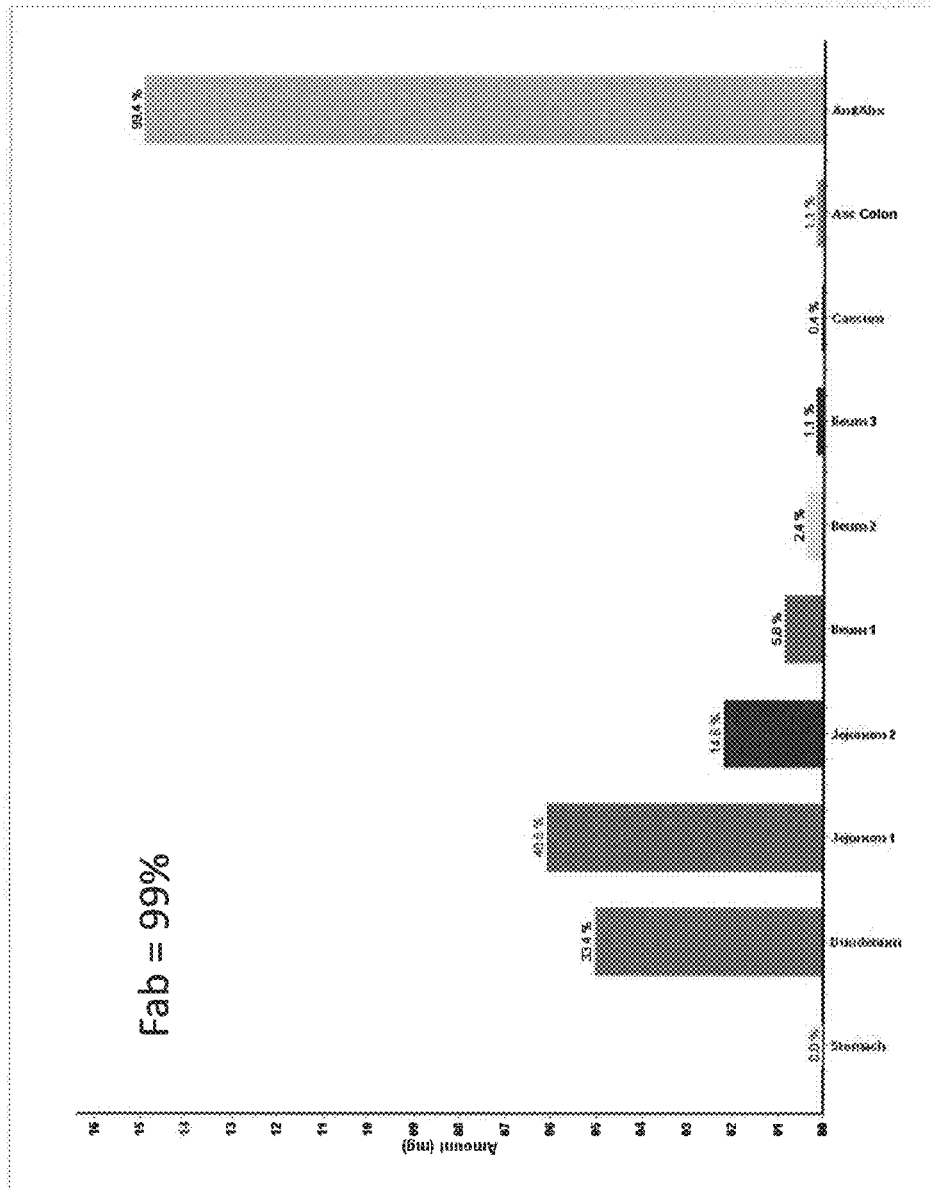


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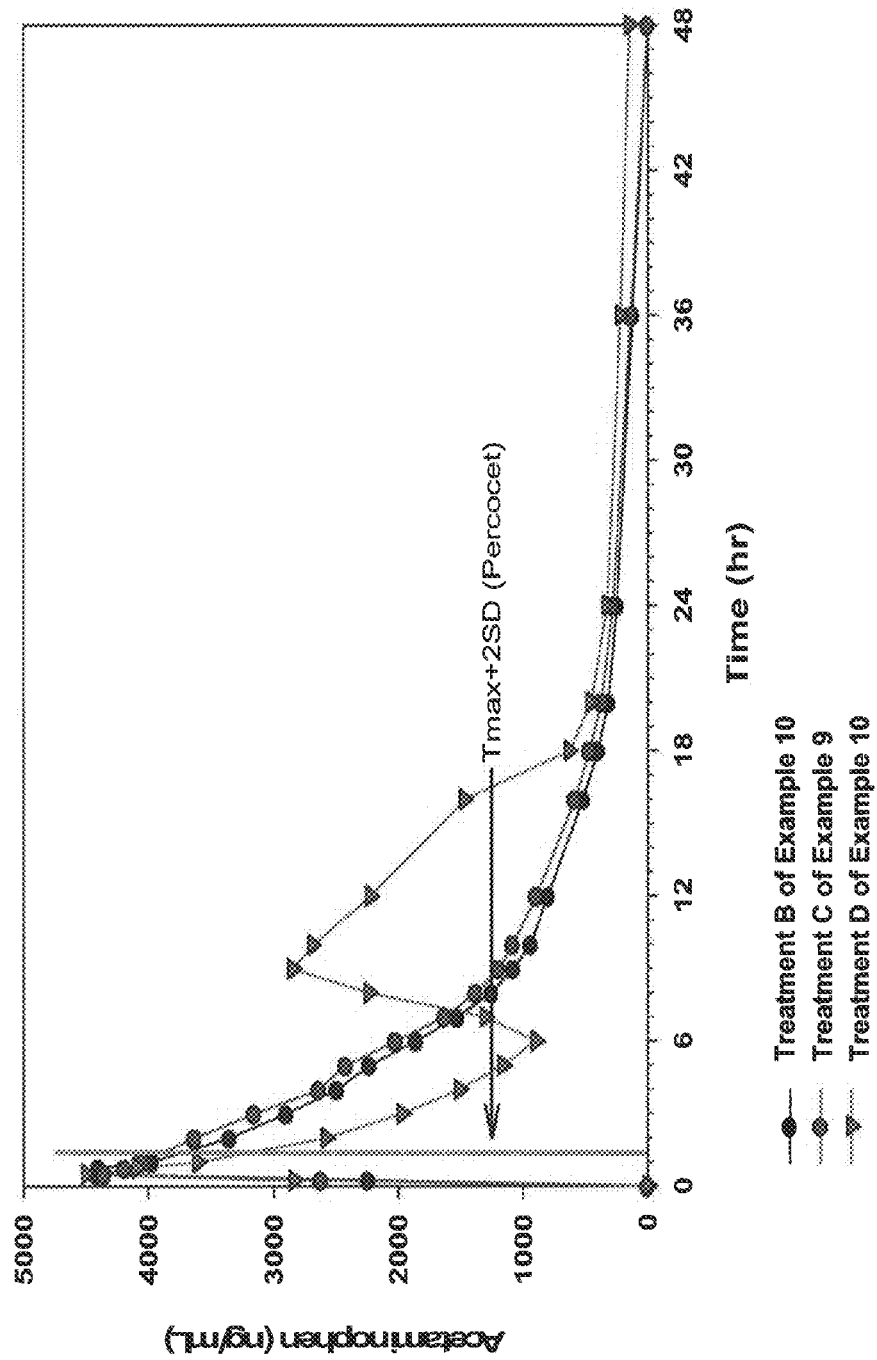


FIG. 29A

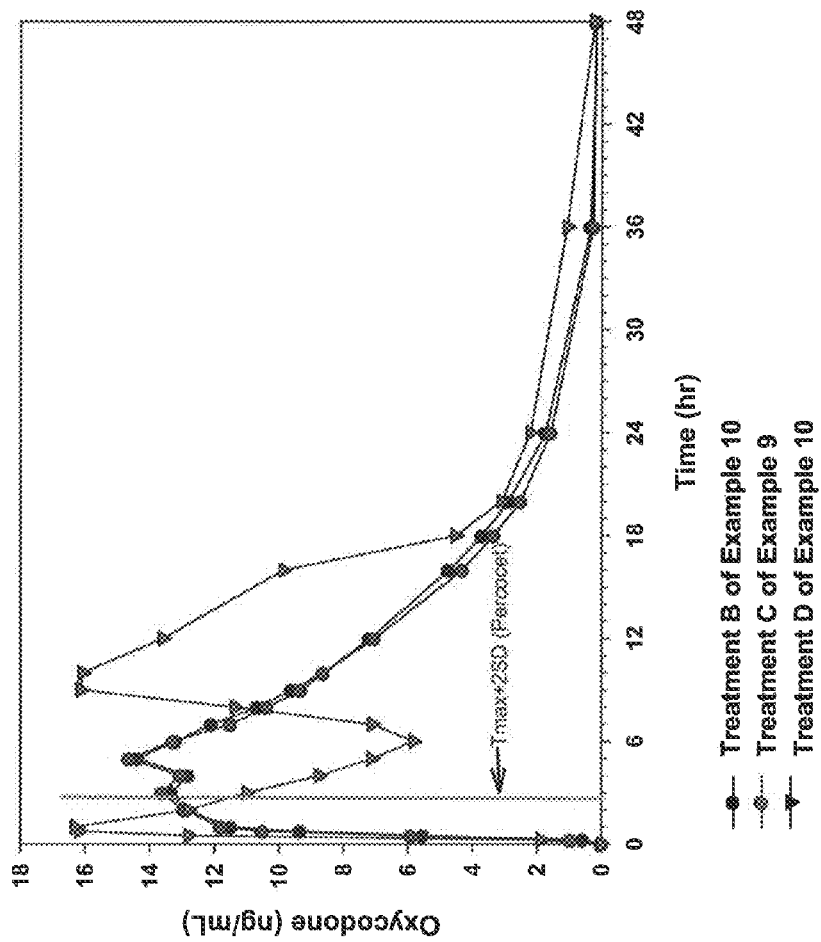


FIG. 29B

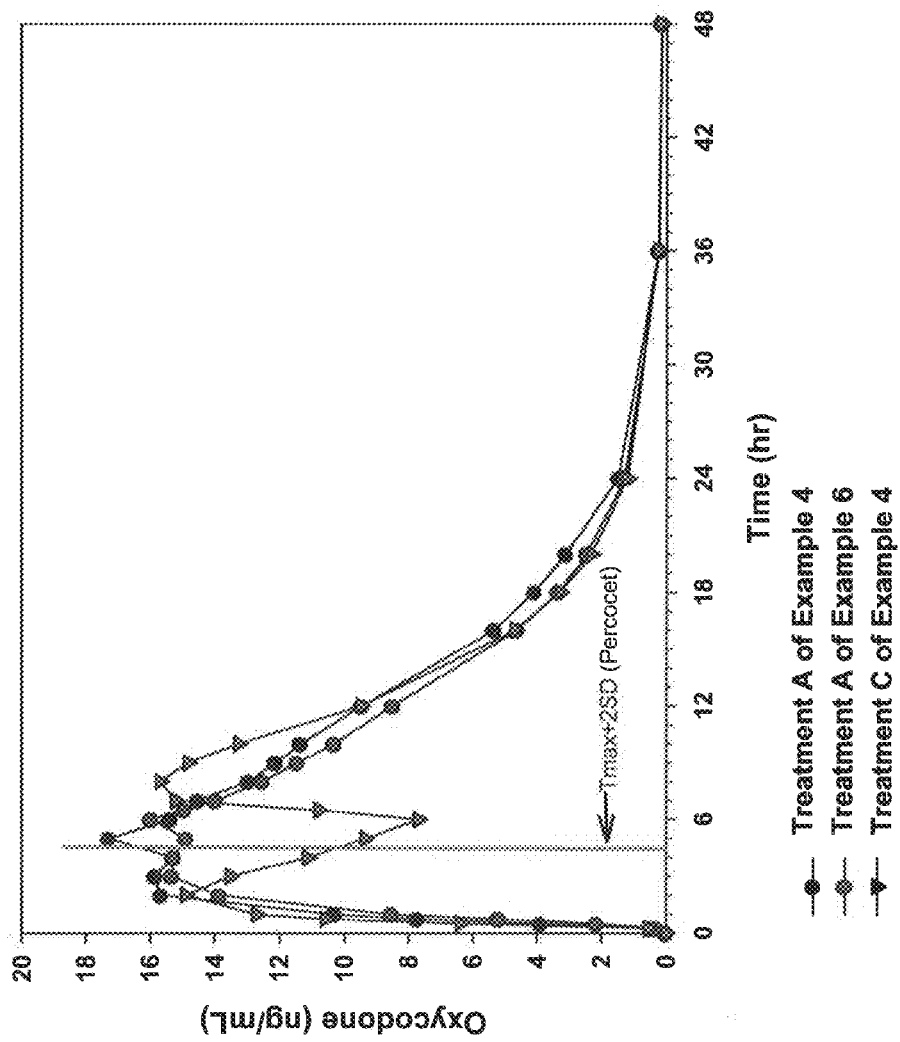


FIG. 30A

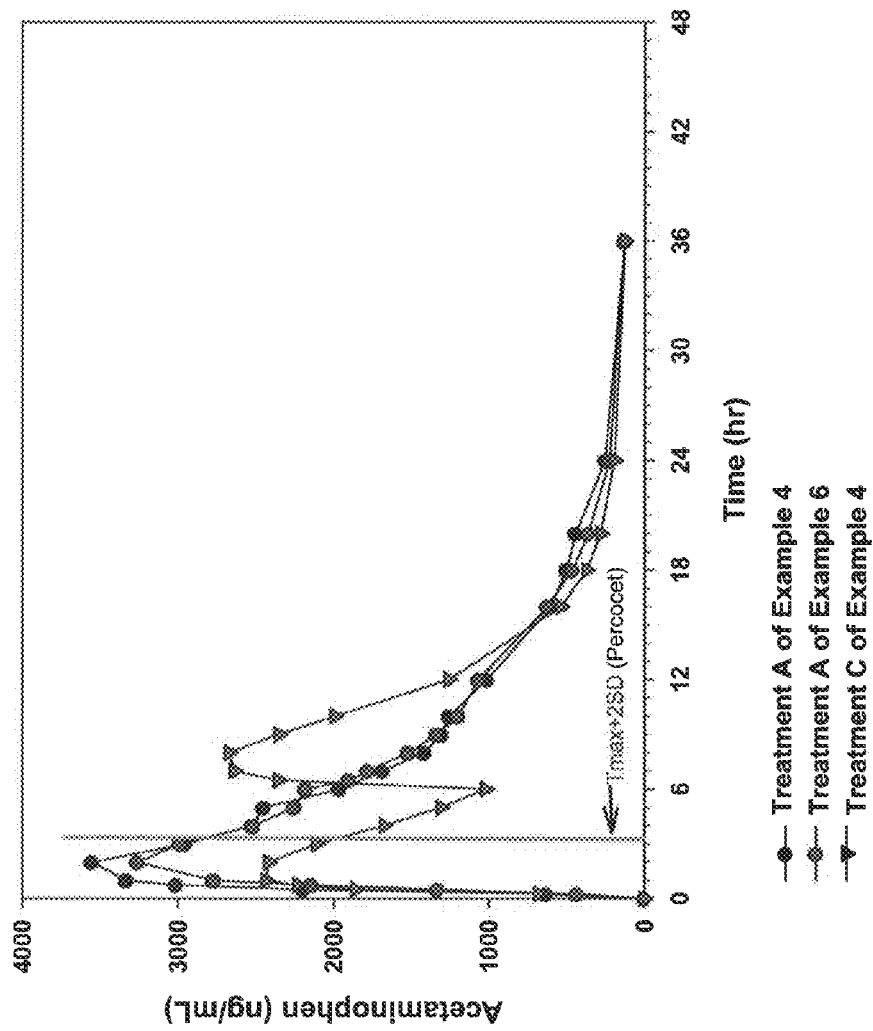


FIG. 30B

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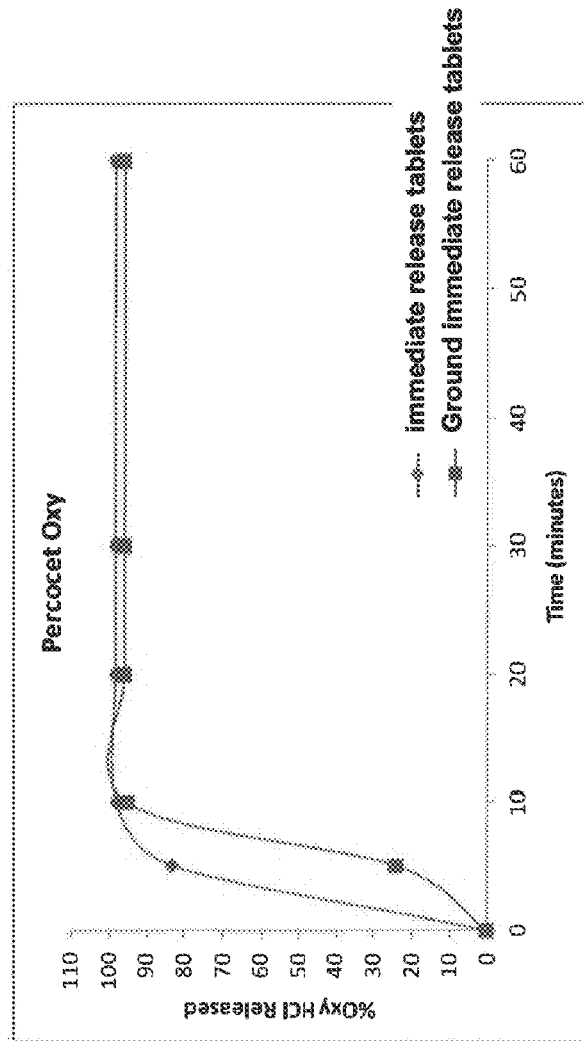


FIG. 31

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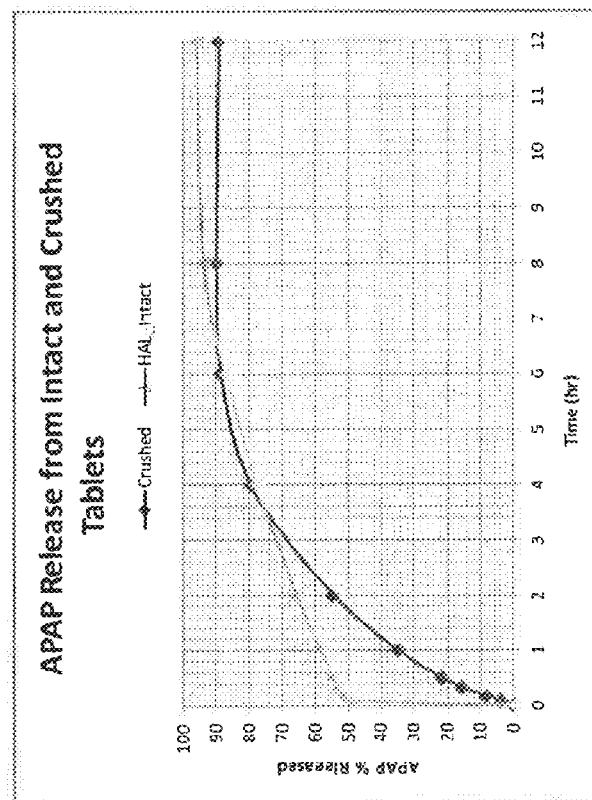


FIG. 32A

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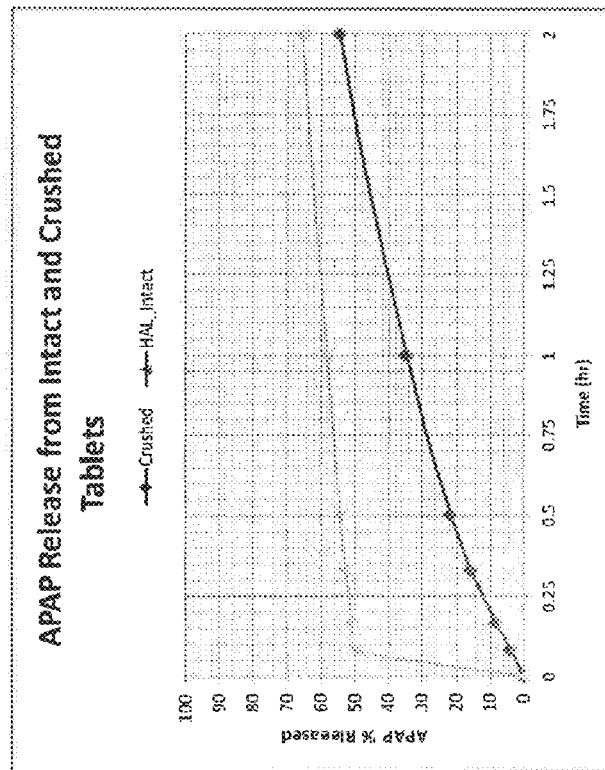


FIG. 32B

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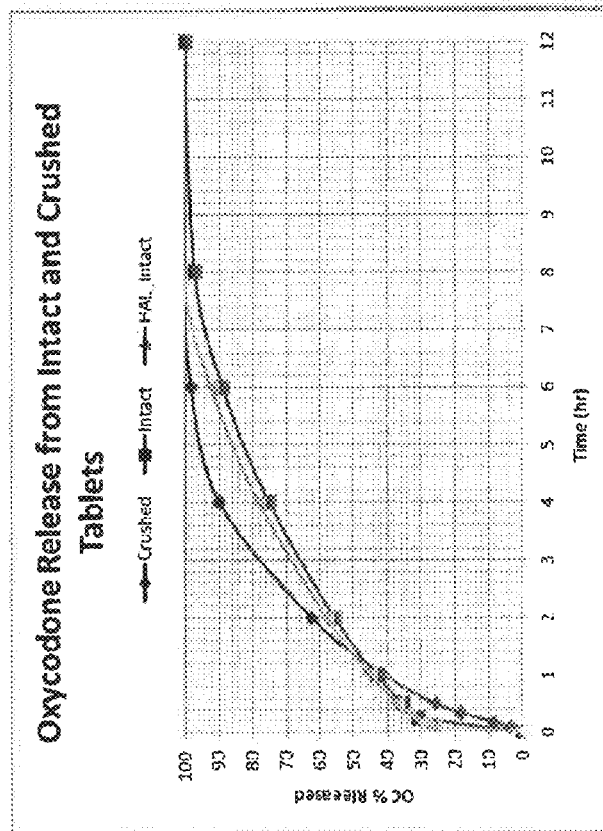


FIG. 33A

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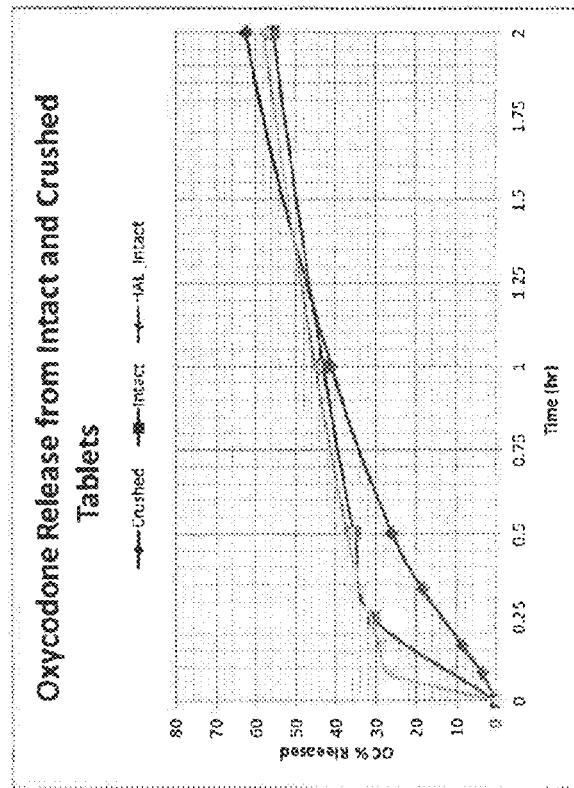


FIG. 33B

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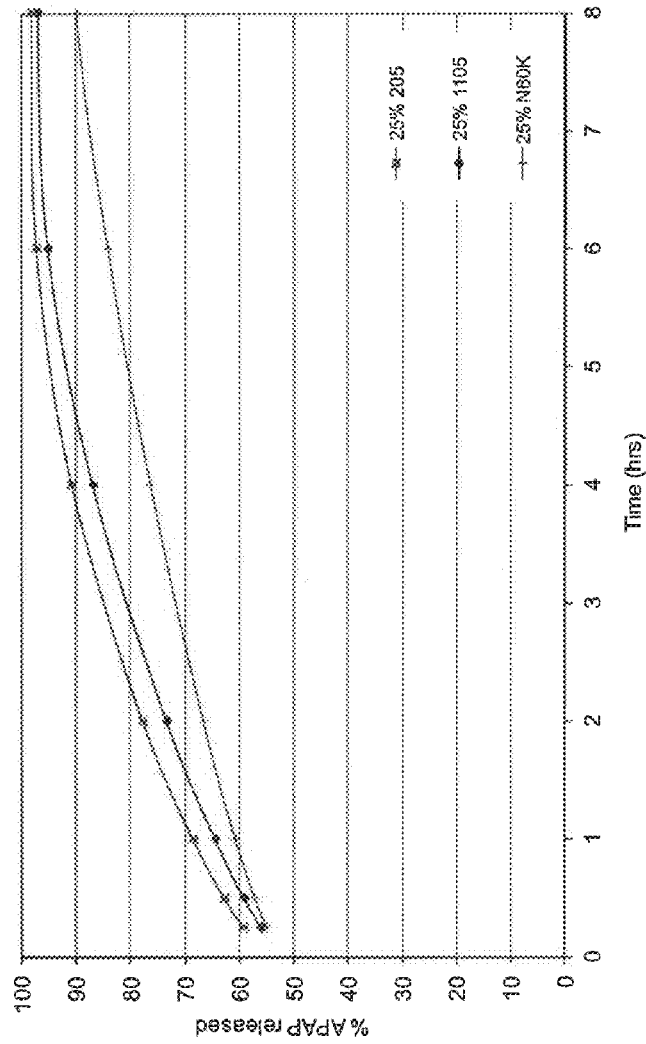


FIG. 34

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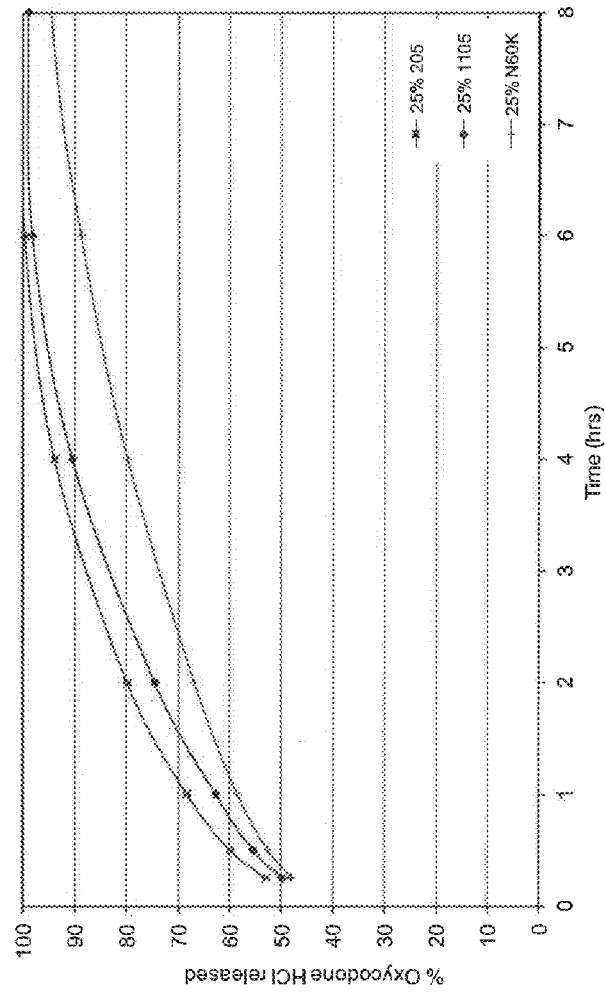


FIG. 35

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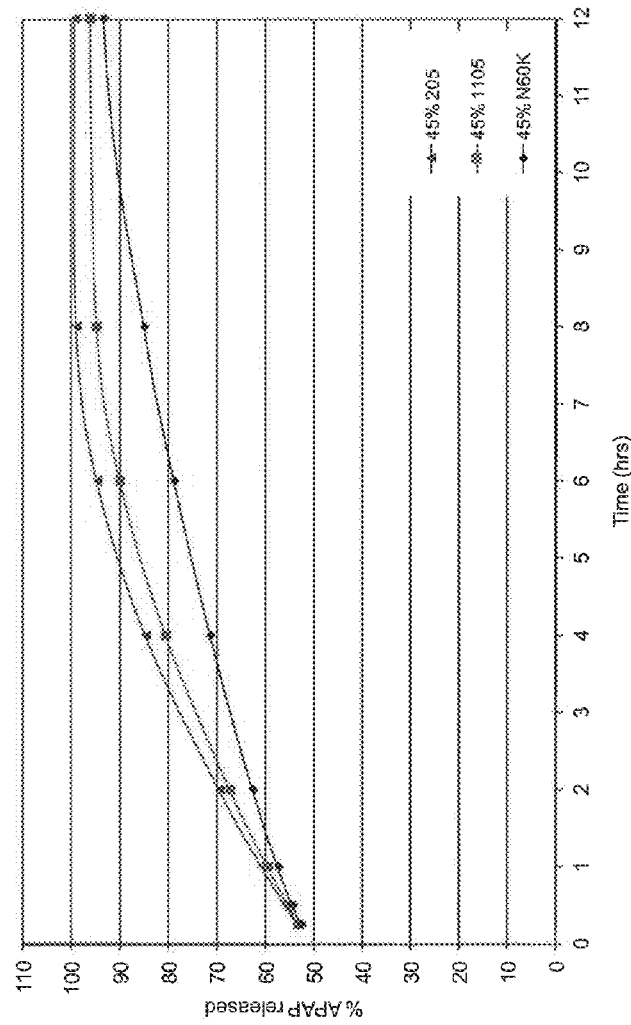


FIG. 36

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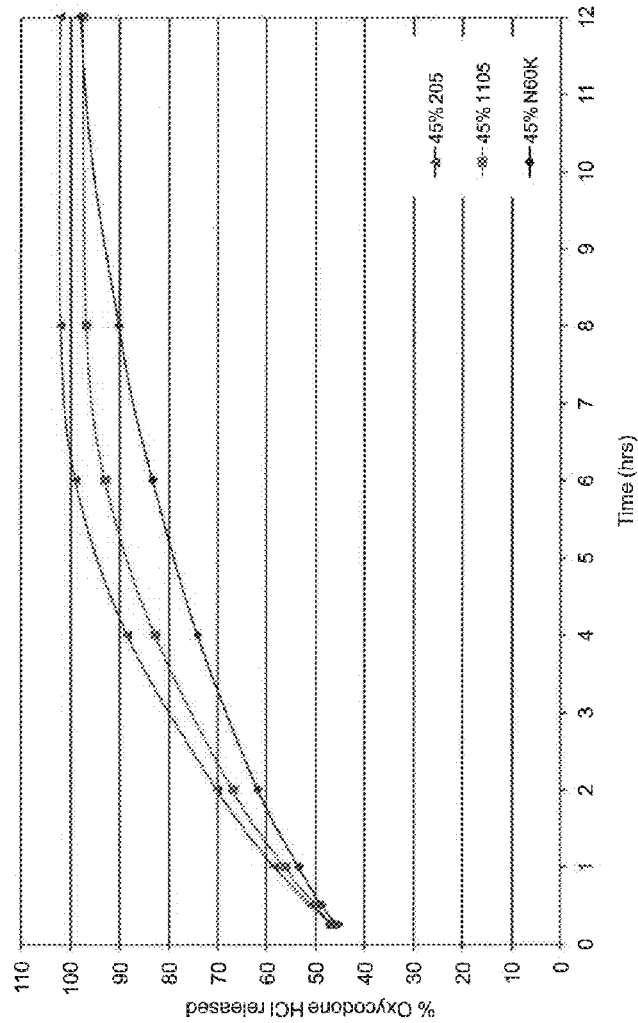


FIG. 37

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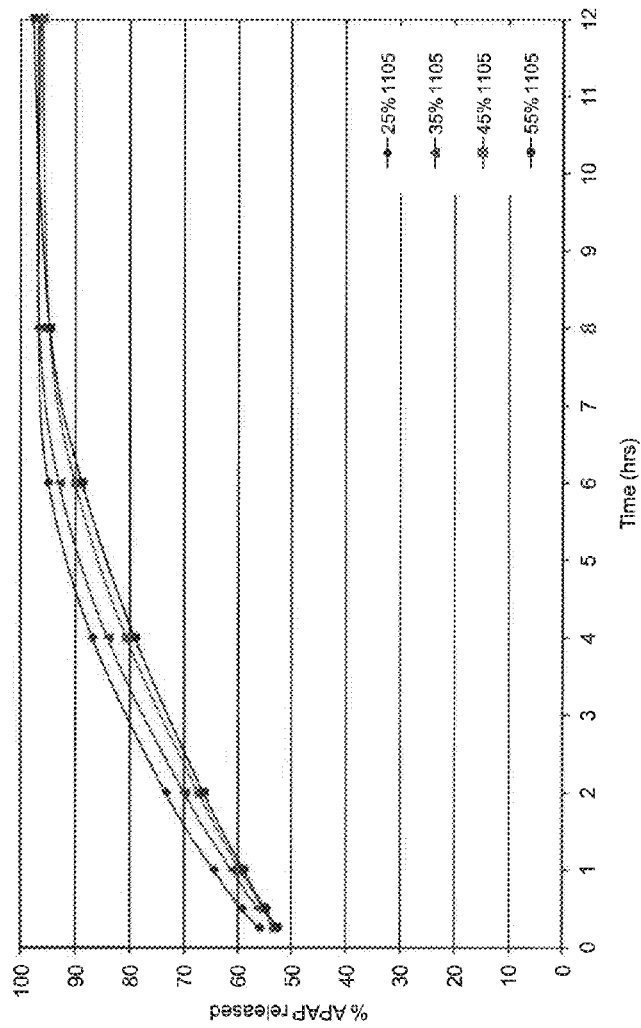


FIG. 38

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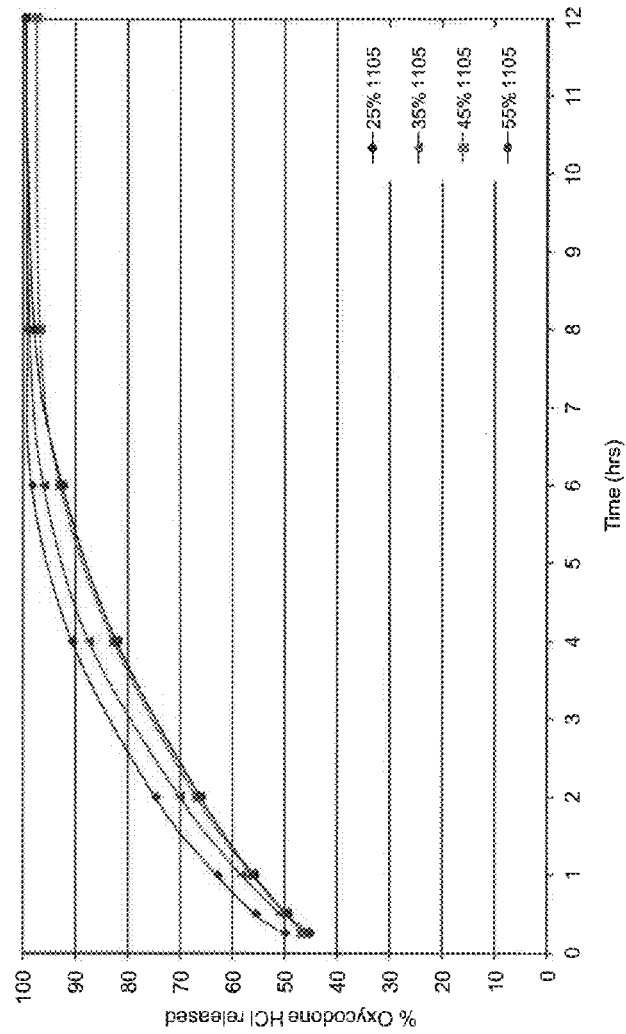


FIG. 39

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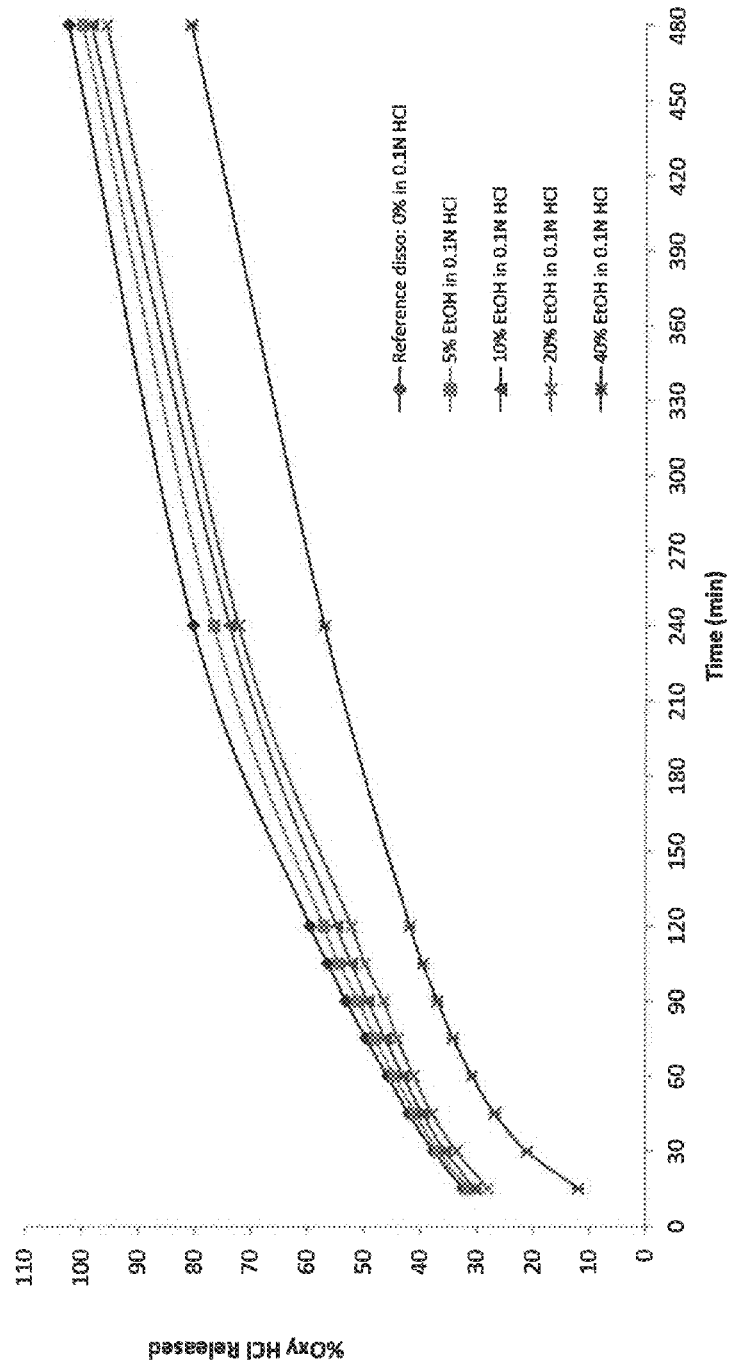


FIG. 40

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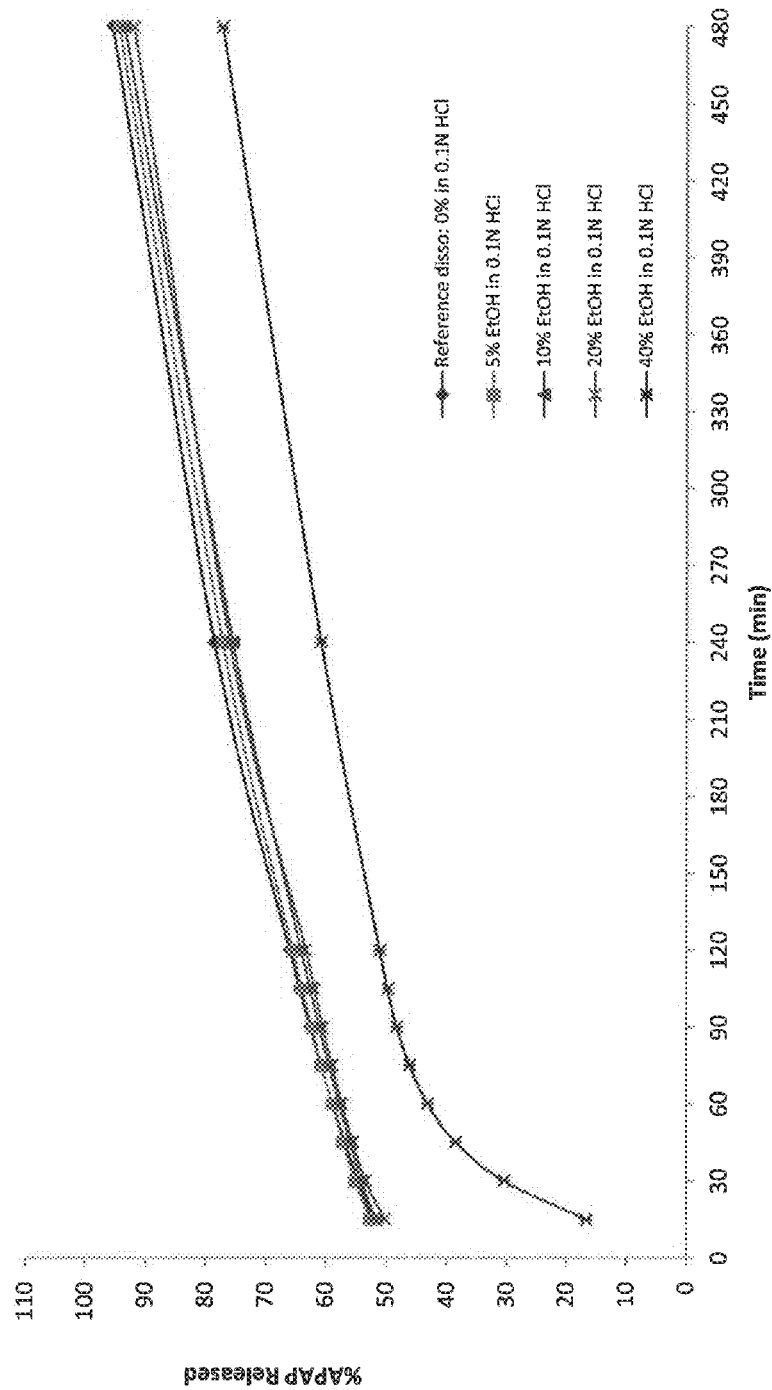


FIG. 41

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**COMBINATION COMPOSITION
COMPRISING OXYCODONE AND
ACETAMINOPHEN FOR RAPID ONSET AND
EXTENDED DURATION OF ANALGESIA**

RELATED CASES

This application claims priority to U.S. Provisional Application No. 61/487,047 filed on May 17, 2011, U.S. Provisional Application No. 61/537,527 filed on Sep. 21, 2011, and U.S. Provisional Application No. 61/606,850 filed on Mar. 5, 2012 which are incorporated herein by reference in their entirety to the full extent permitted by law.

FIELD OF THE INVENTION

The present disclosure relates to an extended release pharmaceutical composition comprising oxycodone and acetaminophen that provides a rapid onset of analgesia, followed by an extended duration of analgesia of about 12 hours.

BACKGROUND OF THE INVENTION

Oral drug administration remains the route of choice for the majority of clinical applications. Modified release (MR) dosage forms that are administered once or twice daily offer advantages over their immediate release (IR) counterparts because they reduce the magnitude of peaks and troughs of drug plasma concentration, provide longer dosing intervals, sustained analgesic effect, and increased patient compliance. These modified release formulations may be referred to as controlled release (CR), sustained release (SR) and/or extended release (ER) etc. For certain types of patients, such as those suffering from pain, these MR products may permit the patient to sleep through the night without having to wake up during the night to take the next dose. Thus, it can significantly increase the quality of life for such patients. Both IR and MR products for pain are widely available in the market. Examples of IR products include those containing NSAIDs, opioids, profens, COX II inhibitors and aspirin (Tylenol, Advil, Celebrex, Vioxx, Aleve, Voltaren). Examples of MR products include those containing NSAIDs and opioids (Tylenol SR, Oxycontin).

Researchers have also combined various classes of pain drugs to provide better analgesia to patients. For example, a combination of acetaminophen-oxycodone hydrochloride is commercially available as Percocet and acetaminophen-hydrocodone bitartrate as Vicodin. In randomized controlled trials, it was shown that the combination product Percocet was statistically superior to MR oxycodone in various outcome measures of pain relief. Other combination products such as Acetaminophen-Hydrocodone and Acetaminophen-Tramadol are either available or described in the literature. It is postulated that the combination of two analgesic drugs with complementary mechanisms of action results in enhanced analgesia due to an additive effect, an "opioid-sparing" effect, and an improved side effect and safety profile. The improved safety profile results from the use of reduced doses of two analgesics with different side-effects rather than an equieffective dose of a single agent.

Acetaminophen is absorbed from the small intestine and primarily metabolized by conjugation, like glucuronidation and sulfation, in the liver to nontoxic, water-soluble compounds that are eliminated in the urine. When the maximum daily dose is exceeded over a prolonged period, metabolism by conjugation becomes saturated, and excess acetaminophen is oxidatively metabolized by cytochrome P450

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(CYP) enzymes (e.g., CYP2E1, 1A2, 2A6, 3A4) to a reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). NAPQI is a reactive free radical with an extremely short half-life that is rapidly inactivated by conjugation with glutathione, which is acting as a sulfhydryl donor. Once the pool of available glutathione is exhausted, the cysteines of cellular proteins become sulfhydryl donors to NAPQI, binding covalently and initiating a cascade of oxidative and cellular damage, resulting in necrosis and, ultimately, liver failure. Thus, avoiding excessive NAPQI formation is an important strategy when using acetaminophen, although to date acetaminophen-sparing has not been an approach any manufacturers have chosen to take. However, due to the prevalence of acetaminophen in many over-the-counter products, it is prudent to consider acetaminophen-sparing precautions when considering combination therapy lasting more than a few days to avoid an inadvertent reduction in glutathione stores.

Thus, various options for pain management are available that are both IR and MR, and contain either a single drug or a combination of analgesics. While these combination products provide the benefits associated with combining two analgesics as described above, both IR and MR, in itself, have a significant disadvantage. IR combination products lack the advantages of MR products described previously. MR combination products lack a significant benefit associated with IR products—rapid onset of analgesia—that is extremely desirable for pain management. Because MR products retard the rate of drug release to sustain the drug effect over prolonged period, release of drug is slow resulting in significant time before effective analgesic drug concentration is attained in the bloodstream. There exists a clinical need for pain management that combines the desirable features of IR and MR in combination pain products.

SUMMARY OF THE INVENTION

Among the various aspects of the present disclosure is a pharmaceutical composition for extended release of oxycodone and acetaminophen comprising at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and at least one extended release component. The composition, when orally administered to a subject, maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition. Additionally, at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration.

A further aspect of the disclosure encompasses a pharmaceutical composition for extended release of oxycodone and acetaminophen comprising (a) at least one immediate release portion comprising oxycodone, acetaminophen or a combination thereof, and (b) at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component, wherein about 30% of the oxycodone in the pharmaceutical composition is released in about 15 minutes and at least about 90% of the acetaminophen in the pharmaceutical composition is released in about 8 hours when measured in 900 ml of 0.1N HCl using a USP type II apparatus at a paddle speed of about 100 rpm and a constant temperature of 37° C.

Yet another aspect of the disclosure provides a pharmaceutical composition for oral administration in the treatment of

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pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component, wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 100 rpm in 900 ml of 0.1N HCl using a USP type II apparatus at a constant temperature of 37° C., about 30%, by weight, of the oxycodone or salt thereof is released at about 15 minutes in the test and at least about 90%, by weight, of the acetaminophen is released at about 8 hours in the test. Further, upon oral administration of a single dose of the composition to a subject in need of analgesia, the composition provides a C_{max} for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg, a C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg, a T_{max} for oxycodone from about 2 hours to about 7 hours, and a T_{max} for acetaminophen from about 0.5 hour to about 6 hours.

In a further aspect of the disclosure provides a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof, and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component; wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg. Moreover, upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 150 rpm in 900 ml of 0.1N HCl using a USP type II apparatus at a constant temperature of 37° C., no more than about 65%, by weight, of the total amount of the oxycodone or salt is released and no more than about 75%, by weight, of the total amount of the acetaminophen is released after 2 hours; from about 65% to about 85%, by weight, of the total amount of the oxycodone or salt is released and from about 70% to about 90%, by weight, of the total amount of the acetaminophen is released after 4 hours; from about 85% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 85% to about 100%, by weight, of the total amount of the acetaminophen is released after 8 hours; and from about 95% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 90% to about 100%, by weight, of the total amount of the acetaminophen is released after 12 hours.

An additional aspect of the disclosure provides for a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component; wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg. And upon oral administration of the composition in an amount of about 15 mg oxycodone or salt and about 650 mg acetaminophen, the composition provides an $AUC_{0-1.7h}$ for acetaminophen of about 5.0 ng·h/mL/mg to about 13.0 ng·h/mL/mg; an $AUC_{1.7-48h}$ for acetaminophen of about 25.0 ng·h/mL/mg to about 75.0 ng·h/mL/mg; an $AUC_{0-2.8h}$ for oxyc-

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odone or salt of about 1.0 ng·h/mL/mg to about 3.0 ng·h/mL/mg; and $AUC_{2.8-48h}$ of about 7.5 ng·h/mL/mg to about 15.0 ng·h/mL/mg.

Still another aspect of the disclosure provides a dosage form comprising (a) an immediate release portion comprising acetaminophen and oxycodone, wherein the immediate release portion comprises, by weight of the immediate release portion, from about 70% to about 80% of acetaminophen and from about 0.5% to about 1% of oxycodone; and (b) an extended release portion comprising acetaminophen, oxycodone, and an extended release polymer, wherein the extended release portion comprises, by weight of the extended release portion, from about 20% to about 40% of acetaminophen, from about 0.5% to about 2% of oxycodone, and from about 30% to about 50% of the extended release polymer.

Another aspect provides a dosage form comprising from about 7.5 mg to about 30 mg of oxycodone and from about 325 mg to about 650 mg of acetaminophen. The dosage form comprises (a) at least one immediate release portion comprising about 25% of the total amount of oxycodone in the composition and about 50% of the total amount of acetaminophen in the composition; and (b) at least one extended release portion comprising about 75% of the total amount of oxycodone in the composition, about 50% of the total amount of acetaminophen in the composition, and about 35% to about 45%, by weight of the at least one extended release portion, of an extended release polymer comprising a polyethylene oxide.

A further aspect of the disclosure provides a method for reducing the risk of acetaminophen-induced hepatic damage in a subject being treated for pain with a dosage regimen that comprises administering to the subject at least two consecutive doses of a pharmaceutical composition comprising oxycodone and acetaminophen. The method comprises (a) administering a first dose of the pharmaceutical composition comprising at least one extended release portion comprising acetaminophen, oxycodone or a combination thereof, and an extended release component to the subject, wherein the composition maintains a therapeutic blood plasma concentration of oxycodone of at least 5 ng/mL from about 0.75 hours to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration; and (b) administering a second dose of the pharmaceutical composition to the subject at about 12 hours after administration of the first dose.

Yet another aspect of the disclosure encompasses a method for treating pain in a subject in need thereof with a pharmaceutical composition that comprises oxycodone and acetaminophen. The method comprises orally administering to the subject an effective amount of the pharmaceutical composition comprising at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component, wherein the composition maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration.

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Other features and aspects of the disclosure are described in detail below.

REFERENCE TO COLOR FIGURES

This application file contains at least one drawing executed in color. Copies of this patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 presents the in vitro release profile of oxycodone from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35 wt % POLYOX® 1105, 45 wt % POLYOX® 1105, or 45 wt % POLYOX® N60K, as indicated.

FIG. 2 shows the in vitro release profile of acetaminophen from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35 wt % POLYOX® 1105, 45 wt % POLYOX® 1105, or 45 wt % POLYOX® N60K, as indicated.

FIG. 3 presents the in vitro release profile of oxycodone from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

FIG. 4 presents the in vitro release profile of acetaminophen from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

FIG. 5 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval.

FIG. 6 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 7 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 8 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 9 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered

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orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

FIG. 10 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

FIG. 11 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

FIG. 12 shows the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

FIG. 13 presents the mean plasma concentrations of oxycodone versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 14 shows the mean plasma concentrations of oxycodone versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 15 presents the mean plasma concentrations of acetaminophen versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 16 shows mean plasma concentrations of acetaminophen versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 17 illustrates the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 150 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 2 hours.

FIG. 18 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 150 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 2 hour period.

FIG. 19 shows the mean plasma concentrations of oxycodone as a function of time by treatment following oral

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administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 20 presents the mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 21 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 22 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 23 shows a deconvolution plot of the biphasic absorption of oxycodone from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of oxycodone is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; squares represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and the immediate release 7.5 oxycodone/325 acetaminophen tablet is shown in a solid line with no symbols.

FIG. 24 presents a deconvolution plot of the biphasic absorption of acetaminophen from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of acetaminophen is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; triangles represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and squares represent the immediate release 7.5 oxycodone/325 acetaminophen product.

FIG. 25 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

FIG. 26 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions.

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Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

FIG. 27A is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation. FIG. 27B is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled. FIG. 27C is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

FIG. 28A is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation. FIG. 28B is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled. FIG. 28C is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

FIG. 29A presents the mean plasma concentrations and Partial AUCs of acetaminophen (e.g., $AUC_{0-1.7h}$ and $AUC_{1.7-48h}$) versus time by treatment: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

FIG. 29B presents the mean plasma concentrations and Partial AUCs of oxycodone (e.g., $AUC_{0-2.8h}$ and $AUC_{2.8-48h}$) versus time by treatment: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

FIG. 30A presents the mean plasma concentrations and Partial AUCs of oxycodone versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

FIG. 30B presents the mean plasma concentrations and Partial AUCs of acetaminophen versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

FIG. 31 presents oxycodone dissolution data from crushed and intact immediate release tablets containing 7.5 mg oxycodone and 325 mg acetaminophen.

FIGS. 32A and 32B present acetaminophen dissolution data from crushed and intact pharmaceutical formulations described herein containing a total of 7.5 mg oxycodone and a total of 325 mg acetaminophen per tablet.

FIGS. 33A and 33B present oxycodone HCl dissolution data from crushed and intact pharmaceutical formulations described herein containing a total of 7.5 mg oxycodone and a total of 325 mg acetaminophen per tablet.

FIG. 34 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total

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of 250 mg acetaminophen. The three pharmaceutical formulations contained 25% by weight POLYOX® 205, 1105, and N-60K, respectively.

FIG. 35 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 34.

FIG. 36 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The three pharmaceutical formulations contained 45% by weight POLYOX® 205, 1105, and N-60K, respectively.

FIG. 37 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 36.

FIG. 38 presents acetaminophen dissolution data for four pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The four pharmaceutical compositions contained 25% by weight, 35% by weight, 45% by weight, and 55% by weight POLYOX® 1105, respectively.

FIG. 39 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 38.

FIG. 40 presents the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 8 hours.

FIG. 41 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 8 hour period.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein is a combination product of oxycodone and acetaminophen that has the desirable attributes of both IR and MR products. The extended release pharmaceutical composition disclosed herein comprises at least one extended release portion and, optionally, at least one immediate release portion. The extended release and immediate release portions may comprise oxycodone, acetaminophen, or combinations thereof. The at least one immediate release portion releases acetaminophen (APAP) and/or oxycodone instantly in an immediate release fashion that provides rapid onset for the attainment of therapeutically effective plasma concentrations within about the first 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition. The at least one extended release portion releases acetaminophen and/or oxycodone in an extended release fashion to maintain plasma concentrations above the minimum effective concentration for about 8-12 hours. In addition, two other important features of this composition are: 1) to allow the plasma concentrations of oxycodone to fall as rapidly as an immediate release formulation to provide the same rate of termination of drug effects as the immediate release product, and 2) to allow the concentrations of APAP to fall even quicker towards the later part of the dosing interval and bring down the levels of APAP lower than those of the immediate release product. The concentrations of APAP in the last quarter of the dosing interval are comparable to the pre-dose concentrations in a multiple dose setting, allowing for the glutathione synthase enzyme cycle to replen-

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ish the body's levels of glutathione to avoid the formation of toxic intermediates with subsequent doses of APAP. Moreover, the concentrations of APAP in the later part of the dosing interval are lower than those present when administered a conventional extended release formulation. This feature has been deliberately introduced to reduce the hepatic injury due to APAP and is termed "APAP time-off".

Abuse potential is a concern with any opioid product. The addition of APAP to the opioid, however, is likely to reduce the amount of abuse by illicit routes of administration, particularly intravenous or intranasal administration. This deterrence is likely due to the bulk (grams) that the APAP provides as well as the relative aqueous insolubility compared to freely soluble opioid salts. Further, APAP is known to be irritating to nasal passages and to make drug abusers sneeze violently when they are trying to snort it. In addition, embodiments disclosed herein may be tamper resistant in that the compositions are difficult to crush for administration intravenously or intranasally; difficult to extract with water or alcohol because the mixture becomes too viscous for injecting or snorting; and resistant to dose dumping in alcohol.

In one embodiment, the pharmaceutical composition disclosed herein, therefore, provides: 1) rapid onset of analgesia within about 15, 30, 45, or 60 minutes after administration of the composition mediated by both oxycodone and APAP, with APAP providing maximal contribution during the early phase; 2) prolonged analgesia for the entire 12 hours period, mainly contributed by oxycodone, with minimal fluctuations during this period; 3) relatively low levels of APAP toward end of dosing interval to allow for recovery of the depleted hepatic glutathione system; 4) low abuse quotient; and 5) abuse deterrence.

Headings included herein are simply for ease of reference, and are not intended to limit the disclosure in any way.

I. Definitions

Compounds useful in the compositions and methods include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, as well as racemic mixtures and pure isomers of the compounds described herein, where applicable.

When introducing elements of the various embodiment(s) of the present disclosure, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

The use of individual numerical values are stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given

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amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words “about” or “approximately” will serve to broaden a particular numerical value or range. Thus, as a general matter, “about” or “approximately” broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term “about” or “approximately.” Consequently, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

The term “abuse quotient” for a pharmaceutical composition as used herein is the numerical value obtained via dividing the C_{max} for a drug by the T_{max} for the same drug. Generally speaking, the abuse quotient provides a means for predicting the degree of addictiveness of a given pharmaceutical composition. Pharmaceutical compositions with lower abuse quotients typically are less addictive compared to pharmaceutical compositions with higher abuse quotients.

The term “active agent” or “drug,” as used herein, refers to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor from eliciting a physiological response.

The term “bioequivalent,” as used herein, refers to two compositions, products or methods where the 90% Confidence Intervals (CI) for AUC, partial AUC and/or C_{max} are between 0.80 to 1.25.

The term “bulk density,” as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

The term “content uniformity,” as used herein refers to the testing of compressed tablets to provide an assessment of how uniformly the micronized or submicron active ingredient is dispersed in the powder mixture. Content uniformity is measured by use of USP Method (General Chapters, Uniformity of Dosage Forms), unless otherwise indicated. A plurality refers to five, ten or more tablet compositions.

The term “friability,” as used herein, refers to the ease with which a tablet will break or fracture. The test for friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of composition abraded or chipped is calculated.

The term “ER” as used herein refers to extended release. The phrases “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” are used interchangeably in this document. Further, as used herein the “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” can be either (i) a discrete part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

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The term “IR” as used herein refers to immediate release. The phrases “immediate release layer,” “IR layer,” “IR portion” and “immediate release portion” are used interchangeably in this document. In addition, as used herein the “immediate release layer,” “IR layer,” “IR portion” and “immediate release portion” can be either (i) a discrete part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

The term “half life” as used herein refers to the time required for a drug’s blood or plasma concentration to decrease by one half. This decrease in drug concentration is a reflection of its excretion or elimination after absorption is complete and distribution has reached an equilibrium or quasi equilibrium state. The half life of a drug in the blood may be determined graphically off of a pharmacokinetic plot of a drug’s blood-concentration time plot, typically after intravenous administration to a sample population. The half life can also be determined using mathematical calculations that are well known in the art. Further, as used herein the term “half life” also includes the “apparent half-life” of a drug. The apparent half life may be a composite number that accounts for contributions from other processes besides elimination, such as absorption, reuptake, or enterohepatic recycling.

“Optional” or “optionally” means that the subsequently described element, component or circumstance may or may not occur, so that the description includes instances where the element, component, or circumstance occurs and instances where it does not.

“Partial AUC” means an area under the drug concentration-time curve (AUC) calculated using linear trapezoidal summation for a specified interval of time, for example, $AUC_{(0-1hr)}$, $AUC_{(0-2hr)}$, $AUC_{(0-4hr)}$, $AUC_{(0-6hr)}$, $AUC_{(0-8hr)}$, $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$, $AUC_{(0-(x)hr)}$, $AUC_{(x-yhr)}$, $AUC_{(T_{max}-t)}$, $AUC_{(0-t)hr}$, $AUC_{(T_{max} \text{ of IR product}+2SD-t)}$, or $AUC_{(0-\infty)}$.

A drug “release rate,” as used herein, refers to the quantity of drug released from a dosage form or pharmaceutical composition per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically measured as an in vitro rate of dissolution, i.e., a quantity of drug released from the dosage form or pharmaceutical composition per unit time measured under appropriate conditions and in a suitable fluid. The specific results of dissolution tests claimed herein are performed on dosage forms or pharmaceutical compositions immersed in 900 mL of 0.1 N HCl using a USP Type II apparatus at a paddle speed of either about 100 rpm or about 150 rpm and a constant temperature of about 37° C. Suitable aliquots of the release rate solutions are tested to determine the amount of drug released from the dosage form or pharmaceutical composition. For example, the drug can be assayed or injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

The terms “subject” or “patient” are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, humans.

The term “tap density” or “tapped density,” as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

II. Pharmaceutical Compositions Comprising Extended and Immediate Release Portions Comprising Oxycodone and Acetaminophen

The present disclosure provides pharmaceutical compositions comprising oxycodone and its pharmaceutical salts and

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acetaminophen. The pharmaceutical composition comprises at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component. The pharmaceutical composition may also comprise at least one immediate release portion comprising oxycodone, acetaminophen, or a combination thereof. The compositions disclosed herein are formulated to deliver therapeutic concentrations of oxycodone and acetaminophen within about the first hour after oral administration and to maintain therapeutic concentrations of oxycodone and acetaminophen for an extended period of time (e.g., 10-12 hours).

The total amount of oxycodone present in the pharmaceutical composition can and will vary. In some embodiments, the total amount of oxycodone present in the pharmaceutical composition may range from about 2 mg to about 160 mg, about 5 mg to about 75 mg, about 5 mg to about 40 mg, or about 10 mg to about 30 mg. In another embodiment, the total amount of oxycodone in the pharmaceutical composition may range from about 5 mg to about 30 mg. In various embodiments, the total amount of oxycodone present in the pharmaceutical composition may be about 5 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, or 160 mg. In one embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 30 mg. In another embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 15 mg. In still another embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 7.5 mg.

The total amount of acetaminophen present in the pharmaceutical composition also may vary. In one embodiment, the total amount of acetaminophen present in the pharmaceutical composition may range from about 80 mg to about 1600 mg. In another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 250 mg to about 1300 mg. In a further embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 300 mg to about 600 mg. In yet another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 325 mg to about 650 mg. In another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 1000 mg, or 1300 mg. In one embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 650 mg. In another embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 500 mg. In yet another embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 325 mg.

(a) Immediate Release Portion

The pharmaceutical composition disclosed herein may comprise at least one immediate release portion. In one embodiment, the at least one immediate release portion may comprise oxycodone. In another embodiment, the at least one immediate release portion may comprise acetaminophen. In a further embodiment, the at least one immediate release portion may comprise oxycodone and acetaminophen.

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The at least one immediate release portion of the pharmaceutical composition is designed to release more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) within about one hour. In one embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 45 min. In another embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 30 min. In a further embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 20 min. In yet another embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 15 min. In an alternate embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 10 min. In yet another embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion may be released in less than about 5 min.

(i) Oxycodone

The at least one immediate release portion of the pharmaceutical composition may comprise oxycodone. The amount of oxycodone in the at least one immediate release portion of the pharmaceutical composition can and will vary. In one embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1 mg to about 40 mg. In a further embodiment, the amount of oxycodone in the at least one immediate release portion of the pharmaceutical composition may range from about 1 mg to about 7.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 7.5 mg to about 15 mg. In yet another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 15 mg to about 40 mg. In various embodiments, the amount of oxycodone in the at least one immediate release portion may be about 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 11.0 mg, 12.0 mg, 13.0 mg, 14.0 mg, 15.0 mg, 20.0 mg, or 40.0 mg. In one embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 7.0 mg and about 8.0 mg, for example, about 7.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may be between about 3.0 mg and about 4.0 mg, for example, about 3.75 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may be between about 1.0 mg and about 2.0 mg, for example, about 1.875 mg.

The amount of oxycodone present in the at least one immediate release portion(s) may be expressed as a percentage (w/w) of the total amount of oxycodone in the pharmaceutical composition. In one embodiment, the at least one immediate release portion may comprise from about 20% to about 30%

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(w/w) of the total amount of oxycodone present in the pharmaceutical composition. In certain embodiments, the percentage of oxycodone present in the at least one immediate release portion of the pharmaceutical composition may be about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% (w/w) of the total amount of oxycodone. In another embodiment, the percentage of oxycodone present in the at least one immediate release portion of the pharmaceutical composition may be about 25% (w/w) of the total amount of oxycodone present in the pharmaceutical composition.

The amount of oxycodone in the at least one immediate release portion also may be expressed as a percentage (w/w) of the total weight of the immediate release portion(s) of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an immediate release portion may range from about 0.2 (w/w) to about 15.0% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In another embodiment, the amount of oxycodone in an immediate release portion may range from about 0.5% (w/w) to about 2% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion may comprise an amount of oxycodone that is approximately 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.25%, 7.5%, 7.75%, 8.0%, 8.25%, 8.5%, 8.75%, 9.0%, 9.25%, 9.5%, 9.75%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In yet another embodiment, the amount of oxycodone in an immediate release portion may be about 0.5% (w/w) to about 1.0% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

In some embodiments, the oxycodone of the at least one immediate release portion(s) of the pharmaceutical composition may be in the form of particles comprising oxycodone and at least one excipient. The at least one immediate release portion, therefore, may comprise particles of oxycodone that are admixed with the acetaminophen and optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety. The oxycodone particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Acetaminophen

The at least one immediate release portion of the pharmaceutical composition may comprise acetaminophen. The amount of acetaminophen in the at least one immediate release portion(s) can and will vary. In one embodiment, the amount of acetaminophen in the at least one immediate release portion of the pharmaceutical composition may range from about 40 mg to about 800 mg. In still another embodi-

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ment, the at least one immediate release portion of the pharmaceutical composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one immediate release portion may comprise from about 125 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 500 mg, 520 mg, 650 mg, or 780 mg. In one embodiment, the at least one immediate release portion may comprise about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 125 mg.

The at least one immediate release portion(s) of the pharmaceutical composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. The amount of acetaminophen in the at least one immediate release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. In one embodiment, the percentage of acetaminophen present in the at least one immediate release portion may be about 50% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition.

The amount of acetaminophen in an immediate release portion(s) of the pharmaceutical composition may range from about 20% (w/w) to about 95% (w/w) of the total weight of such immediate release portion of the composition. In various embodiments, an immediate release portion may comprise an amount of acetaminophen that is approximately about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, or 95% (w/w) of the total weight of such immediate release portion. In one embodiment, the amount of acetaminophen in an immediate release portion may range from about 70% to about 80% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

(iii) Excipients

The at least one immediate release portion(s) of the pharmaceutical composition may further comprise at least one excipient. Suitable excipients include binders, fillers, disintegrants, lubricants, antioxidants, chelating agents, and color agents.

In one embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium

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alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxycellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an immediate release portion of the pharmaceutical composition may range from about 5% to about 10% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the pharmaceutical composition may comprise at least one binder that is present in an amount that is about 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, or 9.0% (w/w) of such immediate release portion of the composition.

In another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an immediate release portion may range from about 1.0% to about 10.0% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the pharmaceutical composition may comprise at least one filler that is present in an amount that is about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.2%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, or 10.0%, of such immediate release portion of the pharmaceutical composition.

In still another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may further comprise a disintegrant. The disintegrant may be selected from the group consisting of croscarmellose sodium, crospovidone, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, low substituted hydroxypropylcellulose, microcrystalline cellulose, and sodium starch glycolate. In one embodiment, the amount of disintegrant in an immediate release portion may range from about 2.0% to about 15.0% (w/w) of the total weight of such immediate release portion. In some embodiments, the amount of disintegrant in an immediate release portion may be about 4.0%, 4.2%, 4.4%, 4.6%, 4.8%, 5.0%, 5.2%, 5.4%, 5.6%, 5.8%, 6.0%, 6.2%, 6.4%, 6.6%, 6.8%, or 7.0% (w/w) of such immediate release portion of the pharmaceutical composition.

In a further embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may further comprise a lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of an immediate release portion. In certain embodiments, the amount of lubricant in at least one immediate release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.55%, 1.6%, 1.65%, 1.7%,

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1.75%, 1.80%, 1.85%, 1.90%, or 2.0% (w/w) of the total weight of such immediate release portion.

In yet another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one antioxidant. Suitable antioxidants include, without limitation, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, and propylgallate. The amount of antioxidant present in an immediate release portion of the pharmaceutical composition may range from about 0.01% to about 4.0% (w/w), or from about 0.02% to about 0.10% (w/w) of the total weight of such immediate release portion. In various embodiments, the amount of antioxidant present in an immediate release portion of the pharmaceutical composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such immediate release portion.

In still another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo) tetraacetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N'',N'''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicycysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N'-tetraacetic acid. In one embodiment, the chelating agent may be the sodium salt of EDTA. The amount of chelating agent present in an immediate release portion of the pharmaceutical composition may range from about 0.001% to about 0.20% (w/w) of such immediate release portion. In some embodiments, the amount of chelating agent present in an immediate release portion of the pharmaceutical composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such immediate release portion.

In an alternate embodiment, the at least one immediate release portion of the pharmaceutical composition may comprise a color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an immediate release portion may range from about 2.0% to about 5.0% (w/w) of the total weight of such immediate release portion of the composition. In other embodiments, the amount of color agent present in an immediate release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of the total weight of such immediate release portion.

(b) Extended Release Portion

The pharmaceutical composition disclosed herein comprises at least one extended release portion. The at least one extended release portion may comprise oxycodone, acetaminophen, or a combination thereof. The extended release por-

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tion(s) further comprise(s) an extended release component. The extended release component may comprise at least one extended release polymer.

The at least one extended release portion of the pharmaceutical composition is designed to release the active agents over an extended period of time. In general, the extended release portion(s) provides release of oxycodone and/or acetaminophen for a period of time ranging from at least about 3 hours (hrs) to at least about 12 hrs. In one embodiment, the extended release portion(s) may release oxycodone and/or acetaminophen over a period of at least about 5 hrs, or over a period at least about 6 hrs. In another embodiment, oxycodone and/or acetaminophen may be released from the extended release portion(s) over a period of at least about 7 hrs, or over a period of at least about 8 hrs. In still another embodiment, the extended release portion(s) may release oxycodone and/or acetaminophen over a period of at least about 9 hrs, or over a period of at least about 10 hrs. In a further embodiment, oxycodone and/or acetaminophen may be released from the extended release portion(s) over a period of at least about 11 hrs, or over a period of at least about 12 hrs.

(i) Oxycodone

The amount of oxycodone present in the at least one extended release portion(s) can and will vary. In one embodiment, the amount of oxycodone in the at least one extended release portion may range from about 1 mg to about 120 mg. In a further embodiment, the at least one extended release portion of the pharmaceutical composition may comprise about 1 mg to about 22.5 mg of oxycodone. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 10 mg to about 30 mg. In yet another embodiment, the amount of oxycodone in the at least one extended release portion may be about 30 mg to about 60 mg. In another embodiment, the at least one extended release portion comprises about 5 mg to about 7 mg of oxycodone. In a further embodiment, the amount of oxycodone may be about 5.625 mg to about 11.25 mg. In an additional embodiment, the amount of oxycodone may be about 10 mg to about 12.5 mg. In a further embodiment, the amount of oxycodone may be about 12 mg to about 18 mg. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 20 mg to about 25 mg. In yet another embodiment, the amount of oxycodone may be about 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 5.625 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10.0 mg, 10.5 mg, 11.0 mg, 11.25 mg, 11.5 mg, 12.0 mg, 12.5 mg, 13.0 mg, 13.5 mg, 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 22.5 mg, or 25 mg. In one embodiment, the amount of oxycodone in the at least one extended release portion may be from about 22 mg to about 23 mg, for example, about 22.5 mg. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 10 mg to about 12 mg, for example, about 11.25 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may be from about 5 mg to about 6 mg, for example, about 5.625 mg.

The amount of oxycodone present in the at least one extended release portion(s) may be expressed as a percentage of the total amount of oxycodone in the pharmaceutical composition. In one embodiment, the at least one extended release portion of the pharmaceutical composition comprises from about 70% to about 80% (w/w) of the total amount of oxycodone present in the pharmaceutical composition. In certain embodiments, the percentage of oxycodone present in the at least one extended release portion of the pharmaceutical com-

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position may be about 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% of the total amount of oxycodone. In one embodiment, the percentage of oxycodone present in the at least one extended release portion of the pharmaceutical composition may be about 75% of the total amount of oxycodone present in the pharmaceutical composition.

The amount of oxycodone in the extended release portion(s) also may be expressed as a percentage of the total weight of the extended release portion(s) of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an extended release portion may range from about 0.5% to about 5.0% (w/w) of the total weight of the such extended release portion of the pharmaceutical composition. In various embodiments, an extended release portion may comprise an amount of oxycodone that is approximately 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, or 4.0% (w/w) of the total weight of such extended release portion of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an extended release portion comprises about 0.5% to about 2% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

In some embodiments, the oxycodone of the extended release portion(s) may be in the form of particles comprising oxycodone and at least one excipient. Thus, the at least one extended release portion may comprise particles of oxycodone which are admixed with the acetaminophen and the extended release component, both of which are detailed below, as well as optional excipients. Suitable oxycodone particles are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety. The oxycodone particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Acetaminophen

The extended release portion(s) of the pharmaceutical composition may comprise acetaminophen. The amount of acetaminophen in the extended release portion(s) of the pharmaceutical composition can and will vary. In one embodiment, the at least one extended release portion of the pharmaceutical composition may comprise an amount of acetaminophen ranging from about 40 mg to about 800 mg. In still another embodiment, the at least one extended release portion of the pharmaceutical composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one extended release portion may comprise from about 125 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one extended release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155

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mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 500 mg, 520 mg, 650 mg, or 780 mg. In one embodiment, the at least one extended release portion comprises about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 125 mg.

The extended release portion(s) of the pharmaceutical composition may comprise from about 40% to about 60% of the total amount of acetaminophen present in the pharmaceutical composition. The amount of acetaminophen in the at least one extended release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. In one embodiment, the percentage of acetaminophen present in the extended release portion(s) of the pharmaceutical composition may be about 50% (w/w) of the total amount of acetaminophen.

The amount of acetaminophen in an extended release portion of the pharmaceutical composition may range from about 15% to about 60% (w/w) of the total weight of such extended release portion of the pharmaceutical composition. In various embodiments, an extended release portion may comprise an amount of acetaminophen that is approximately about 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 30%, 32%, 35%, 37%, 40%, 42%, 45%, 47%, 50%, 52%, or 55% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of acetaminophen in an extended release portion may range from about 20% to about 40% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

(iii) Extended Release Component

The extended release portion(s) of the pharmaceutical composition also comprise(s) an extended release component. Suitable extended release components include polymers, resins, hydrocolloids, hydrogels, and the like.

In one embodiment, the extended release component may comprise at least one extended release polymer. Suitable polymers for inclusion in the at least one extended release portion of the pharmaceutical composition may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, such as random copolymers, block copolymers, and graft copolymers. Suitable hydrophilic polymers include, but are not limited to: polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers; cellulosic polymers, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, microcrystalline cellulose, and polysaccharides and their derivatives; acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate; maleic anhy-

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dride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); polyalkylene oxides; poly(olefinic alcohols) such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; xanthan gum; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate. The polymers may be used individually or in combination. Certain combinations will often provide a more controlled release of oxycodone and acetaminophen than their components when used individually. Suitable combinations include cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum, and poly(ethylene oxide) combined with xanthan gum.

In one embodiment, the extended release polymer(s) may be a cellulosic polymer, such as an alkyl substituted cellulose derivative as detailed above. In terms of their viscosities, one class of exemplary alkyl substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C.

In one embodiment, the extended release polymer(s) may be a polyalkylene oxide. In another aspect, the polyalkylene oxide may be poly(ethylene)oxide. In a further embodiment, the poly(ethylene)oxide may have an approximate molecular weight between 500,000 Daltons (Da) to about 10,000,000 Da or about 900,000 Da to about 7,000,000 Da. In yet a further embodiment, the poly(ethylene) oxide may have a molecular weight of approximately 600,000 Da, 700,000 Da, 800,000 Da, 900,000 Da, 1,000,000 Da, 2,000,000 Da, 3,000,000 Da, 4,000,000 Da, 5,000,000 Da, 6,000,000 Da, 7,000,000 Da, 8,000,000 Da, 9,000,000 Da, or 10,000,000 Da.

In another embodiment, the polyethylene oxide may be any desirable grade of POLYOX™ or any combination thereof. By way of example and without limitation, the POLYOX™ grade may be WSR N-10, WSR N-80, WSR N-750, WSR 205, WSR 1105, WSR N-12K, WSR N-60K, WSR-301, WSR Coagulant, WSR-303, WSR-308, WSR N-3000, UCARFLOC Polymer 300, UCARFLOC Polymer 302, UCARFLOC Polymer 304, and UCARFLOC Polymer 309. In one embodiment, the polyethylene oxide may have an average molecular weight of from about 100,000 Da to about 8,000,000 Da. In another embodiment, the polyethylene oxide may have an average molecular weight of about 100,000 Da, about 200,000 Da, about 300,000 Da, about 400,000 Da, about 600,000 Da, about 900,000 Da, about 1,000,000 Da, about 2,000,000 Da, about 4,000,000 Da, about 5,000,000 Da, about 7,000,000 Da, or about 8,000,000 Da. In still another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units ($-\text{CH}_2\text{CH}_2\text{O}-$) of about 2,000 to about 160,000. In yet

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another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units of about 2,275, about 4,500, about 6,800, about 9,100, about 14,000, about 20,000, about 23,000, about 45,000, about 90,000, about 114,000, or about 159,000.

The release profile of the extended release pharmaceutical composition disclosed herein will depend partially upon the molecular weight of the extended release polymer(s). In certain embodiments, the polymers are of a moderate to high molecular weight (900,000 Da to 4,000,000 Da) to control release of oxycodone and/or acetaminophen from the composition via diffusion of the active agent(s) out of the polymer and/or erosion of the polymer. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of about 900,000 Da to about 2,000,000 Da. Using a lower molecular weight ("MW") polyethylene oxide, such as POLYOX® 1105 (900,000 MW), the release rates for both drugs are higher. Using a higher molecular weight polyethylene oxide (such as POLYOX® N-60K (2,000,000 MW) or POLYOX® WSR-301 (4,000,000 MW) reduces the rate of release for both drugs. In another embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight is utilized so that the viscosity of a 2% aqueous solution is about 4000 cps to greater than about 100,000 cps.

The release profile of the extended release pharmaceutical composition disclosed herein may also depend upon the amount of the extended release polymer(s) in the pharmaceutical composition. In general, the release rates for oxycodone and/or acetaminophen may be decreased by increasing the amount of the extended release polymer(s) in the pharmaceutical composition. By way of example and without limitation, the release profile of acetaminophen and oxycodone may be decreased by increasing the amount of POLYOX® 1105 from about 25% by weight of the ER portion to about 35% by weight of the ER portion.

The amount of extended release polymer or polymers present in the extended release portion(s) of the pharmaceutical composition can and will vary. In one embodiment, the polymer present in an extended release portion of the pharmaceutical composition may range from about 15% to about 70% (w/w), or about 20% to about 60% (w/w), or about 25% to about 55% (w/w) of the total weight of such extended release portion of the dosage form. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 30% to about 50% (w/w) of the total weight of such extended release portion. In still another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 35% to about 45% (w/w) of the total weight of such extended release portion. In yet another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 30%, 35%, 40%, 45%, 50%, 55%, or 60% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 35% (w/w) of the total weight of such extended release portion. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 45% (w/w) of the total weight of such extended release portion. In one embodiment, the ER layer swells upon imbibition of fluid to a size which is about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% larger than the size of the ER layer prior to imbibition of fluid. In another embodiment, the ER layer swells upon imbibition

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of fluid to a size at least about 25% larger than the size of the ER layer prior to imbibition of fluid within about 15 minutes of the start of fluid imbibition. In still another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 100% larger than the size of the ER layer prior to imbibition of fluid within about 45 min, 50 min, 60 min, 75 min, or 90 min of the start of fluid imbibitions.

(iv) Excipients

The extended release portion(s) of the pharmaceutical composition may further comprise at least one excipient. Suitable excipients include binders, fillers, lubricants, anti-oxidants, chelating agents, and color agents.

In one embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxylcellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an extended release portion of the pharmaceutical composition may range from about 0.5% to about 8.0% (w/w) of such extended release portion. In various embodiments, an extended release portion of the pharmaceutical composition may comprise at least one binder that is present in an amount that is about 0.5%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, or 8.0% (w/w) of such extended release portion of the dosage form.

In another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an extended release portion may range from about 2% to about 50% (w/w) of the total weight of such extended release portion. In various embodiments, an extended release portion of the pharmaceutical composition may comprise at least one filler that is present in an amount that is about 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, or 45% (w/w) of such extended release portion of the dosage form.

In a further embodiment, the extended release portion(s) of the pharmaceutical composition may further comprise a lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of such extended release portion. In certain embodiments, the amount of lubricant in an extended release portion may be about 0.25%, 0.5%, 0.75%, 1.0%,

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1.5%, 1.75%, 1.80%, 1.85%, 1.90%, or 2.0% (w/w) of the total weight of such extended release portion.

In yet another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one antioxidant. Suitable antioxidants include, without limit, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, and propylgallate. The amount of antioxidant present in an extended release portion of the pharmaceutical composition may range from about 0.01% to about 4.0%, or from about 0.02% to about 0.10% (w/w). In various embodiments, the amount of antioxidant present in an extended release portion of the pharmaceutical composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such extended release portion.

In still another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetracetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetracetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetracetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N,N',N'-tetracetic acid. In one embodiment, the chelating agent is the sodium salt of EDTA. The amount of chelating agent present in an extended release portion of the pharmaceutical composition may range from about 0.001% to about 0.20% (w/w) of such extended release portion. In some embodiments, the amount of chelating agent present in an extended release portion of the pharmaceutical composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such extended release portion.

In an alternate embodiment, the extended release portion(s) of the pharmaceutical composition may comprise a color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an extended release portion may range from about 2.0% to about 5.0% (w/w) of such extended release portion of the dosage form. In other embodiments, the amount of color agent present in an extended release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of such extended release portion.

(c) Dosage Forms of the Pharmaceutical Composition

The physical form of the pharmaceutical composition disclosed herein can and will vary. In general, the pharmaceutical composition is a solid dosage form comprising at least one extended release portion and, optionally, at least one immediate release portion. Suitable solid dosage forms include tablets, caplets, capsules, encapsulated beads, and gelscaps. Non-limiting types of tablets include coated tablets, uncoated

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tablets, bilayer tablets, multiparticulate tablets, monolithic tablets, matrix tablets, compressed tablets, and molded tablets. Non-limiting types of capsules include hard capsules and multi-layer capsules.

In one embodiment, the dosage form may be a capsule. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, hard cellulose capsules, and hydrogel capsules. In one example, the core of the capsule may comprise the at least one extended release portion and the shell of the capsule may comprise the at least one immediate release portion of the composition. In another example, the core of the capsule may comprises one extended release portion, comprising oxycodone, acetaminophen and an extended release component, and the shell of the capsule may comprise one immediate release portion of the composition comprising oxycodone and acetaminophen. In yet another example, the core of the capsule may comprise two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and the shell of the capsule may comprise two immediate release portions of the composition, each comprising one of the oxycodone and the acetaminophen. In still another embodiment, the dosage form may be a sustained release capsule comprising the oxycodone or the acetaminophen and exhibiting immediate release and/or extended release properties.

In another embodiment, the dosage form may be a tablet comprising at least one extended release portion and at least one immediate release portion. The at least one immediate release portion may be adjacent to, abutting, or surrounding the at least one extended release portion. In one embodiment, the dosage form may be a bilayer tablet comprising one extended release layer comprising the oxycodone and the acetaminophen and one immediate release layer comprising the oxycodone and the acetaminophen. The bilayer tablet may comprise a coating. In another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the oxycodone and the acetaminophen, and one immediate release portion comprising both the oxycodone and the acetaminophen. In yet another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the oxycodone and the acetaminophen, and two immediate release portions, each comprising one of the oxycodone and the acetaminophen. In still another embodiment, the dosage form may be a sustained release tablet comprising the oxycodone and/or acetaminophen and exhibiting immediate release and/or extended release properties.

In certain embodiments, the tablet may have a friability of no greater than about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.7% or 1.0%. In another embodiment, the tablet may have a friability of greater than 0 but less than about 1.0%, greater than 0 but less than about 0.5%, greater than 0 but less than about 0.3%, or greater than 0 but less than about 0.2%. In still another embodiment, the tablet may have a friability of zero.

In another embodiment, the tablet may have a hardness of at least about 10 Kilopond (also known as kilopons) (kp). In some embodiments, the tablet may have a hardness of about 9 kp to about 25 kp, or about 12 kp to about 20 kp. In further embodiments, the tablet may have a hardness of about 11 kp, 12 kp, 13 kp, 14 kp, 15 kp, 16 kp, 17 kp, 18 kp, 19 kp, or 20 kp.

In additional embodiments, the tablet may have a content uniformity of from about 85 to about 115 percent by weight or from about 90 to about 110 percent by weight, or from about 95 to about 105 percent by weight. In other embodiments, the

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content uniformity may have a relative standard deviation (RSD) equal to or less than about 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1.0%, or 0.5%.

In still other embodiments, prior to administration to a patient or immersion in fluid, the pharmaceutical composition may have (i) a length of approximately 18 mm, 18.01 mm, 18.02 mm, 18.03 mm, 18.04 mm, 18.05 mm, 18.06 mm, 18.07 mm, 18.08 mm, 18.09 mm, 18.1 mm, 18.11 mm, 18.12 mm, 18.13 mm, 18.14 mm, 18.15 mm, 18.16 mm, 18.17 mm, 18.18 mm, 18.19 mm, 18.2 mm, 18.21 mm, 18.22 mm, 18.23 mm, 18.24 mm, 18.25 mm, 18.26 mm, 18.27 mm, 18.28 mm, 18.29 mm, 18.3 mm, 18.31 mm, 18.32 mm, 18.33 mm, 18.34 mm, 18.35 mm, 18.36 mm, 18.37 mm, 18.38 mm, 18.39 mm, 18.4 mm, 18.41 mm, 18.42 mm, 18.43 mm, 18.44 mm, 18.45 mm, 18.46 mm, 18.47 mm, 18.48 mm, 18.49 mm, 18.5 mm, 18.51 mm, 18.52 mm, 18.53 mm, 18.54 mm, 18.55 mm, 18.56 mm, 18.57 mm, 18.58 mm, 18.59 mm, 18.6 mm, 18.61 mm, 18.62 mm, 18.63 mm, 18.64 mm, 18.65 mm, 18.66 mm, 18.67 mm, 18.68 mm, 18.69 mm, 18.7 mm, 18.71 mm, 18.72 mm, 18.73 mm, 18.74 mm, 18.75 mm, 18.76 mm, 18.77 mm, 18.78 mm, 18.79 mm, 18.8 mm, 18.81 mm, 18.82 mm, 18.83 mm, 18.84 mm, 18.85 mm, 18.86 mm, 18.87 mm, 18.88 mm, 18.89 mm, 18.9 mm, 18.91 mm, 18.92 mm, 18.93 mm, 18.94 mm, 18.95 mm, 18.96 mm, 18.97 mm, 18.98 mm, 18.99 mm, 19 mm, 19.01 mm, 19.02 mm, 19.03 mm, 19.04 mm, 19.05 mm, 19.06 mm, 19.07 mm, 19.08 mm, 19.09 mm, 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, 19.3 mm, 19.31 mm, 19.32 mm, 19.33 mm, 19.34 mm, 19.35 mm, 19.36 mm, 19.37 mm, 19.38 mm, 19.39 mm, 19.4 mm, 19.41 mm, 19.42 mm, 19.43 mm, 19.44 mm, 19.45 mm, 19.46 mm, 19.47 mm, 19.48 mm, 19.49 mm, 19.5 mm, 19.51 mm, 19.52 mm, 19.53 mm, 19.54 mm, 19.55 mm, 19.56 mm, 19.57 mm, 19.58 mm, 19.59 mm, 19.6 mm, 19.61 mm, 19.62 mm, 19.63 mm, 19.64 mm, 19.65 mm, 19.66 mm, 19.67 mm, 19.68 mm, 19.69 mm, 19.7 mm, 19.71 mm, 19.72 mm, 19.73 mm, 19.74 mm, 19.75 mm, 19.76 mm, 19.77 mm, 19.78 mm, 19.79 mm, 19.8 mm, 19.81 mm, 19.82 mm, 19.83 mm, 19.84 mm, 19.85 mm, 19.86 mm, 19.87 mm, 19.88 mm, 19.89 mm, 19.9 mm, 19.91 mm, 19.92 mm, 19.93 mm, 19.94 mm, 19.95 mm, 19.96 mm, 19.97 mm, 19.98 mm, 19.99 mm, or 20 mm as measured on the major axis, (ii) a width of approximately 11 mm, 11.01 mm, 11.02 mm, 11.03 mm, 11.04 mm, 11.05 mm, 11.06 mm, 11.07 mm, 11.08 mm, 11.09 mm, 11.1 mm, 11.11 mm, 11.12 mm, 11.13 mm, 11.14 mm, 11.15 mm, 11.16 mm, 11.17 mm, 11.18 mm, 11.19 mm, 11.2 mm, 11.21 mm, 11.22 mm, 11.23 mm, 11.24 mm, 11.25 mm, 11.26 mm, 11.27 mm, 11.28 mm, 11.29 mm, 11.3 mm, 11.31 mm, 11.32 mm, 11.33 mm, 11.34 mm, 11.35 mm, 11.36 mm, 11.37 mm, 11.38 mm, 11.39 mm, 11.4 mm, 11.41 mm, 11.42 mm, 11.43 mm, 11.44 mm, 11.45 mm, 11.46 mm, 11.47 mm, 11.48 mm, 11.49 mm, 11.5 mm, 11.51 mm, 11.52 mm, 11.53 mm, 11.54 mm, 11.55 mm, 11.56 mm, 11.57 mm, 11.58 mm, 11.59 mm, 11.6 mm, 11.61 mm, 11.62 mm, 11.63 mm, 11.64 mm, 11.65 mm, 11.66 mm, 11.67 mm, 11.68 mm, 11.69 mm, 11.7 mm, 11.71 mm, 11.72 mm, 11.73 mm, 11.74 mm, 11.75 mm, 11.76 mm, 11.77 mm, 11.78 mm, 11.79 mm, 11.8 mm, 11.81 mm, 11.82 mm, 11.83 mm, 11.84 mm, 11.85 mm, 11.86 mm, 11.87 mm, 11.88 mm, 11.89 mm, 11.9 mm, 11.91 mm, 11.92 mm, 11.93 mm, 11.94 mm, 11.95 mm, 11.96 mm, 11.97 mm, 11.98 mm, 11.99 mm, 12 mm, 12.01 mm, 12.02 mm, 12.03 mm, 12.04 mm, 12.05 mm, 12.06 mm, 12.07 mm, 12.08 mm, 12.09 mm, 12.1 mm, 12.11 mm, 12.12 mm, 12.13 mm, 12.14 mm, 12.15 mm, 12.16 mm, 12.17 mm, 12.18 mm, 12.19 mm, 12.2 mm, 12.21 mm, 12.22 mm, 12.23 mm, 12.24 mm, 12.25 mm, 12.26 mm, 12.27 mm,

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12.28 mm, 12.29 mm, 12.3 mm, 12.31 mm, 12.32 mm, 12.33 mm, 12.34 mm, 12.35 mm, 12.36 mm, 12.37 mm, 12.38 mm, 12.39 mm, 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, 12.5 mm, 12.51 mm, 12.52 mm, 12.53 mm, 12.54 mm, 12.55 mm, 12.56 mm, 12.57 mm, 12.58 mm, 12.59 mm, 12.6 mm, 12.61 mm, 12.62 mm, 12.63 mm, 12.64 mm, 12.65 mm, 12.66 mm, 12.67 mm, 12.68 mm, 12.69 mm, 12.7 mm, 12.71 mm, 12.72 mm, 12.73 mm, 12.74 mm, 12.75 mm, 12.76 mm, 12.77 mm, 12.78 mm, 12.79 mm, 12.8 mm, 12.81 mm, 12.82 mm, 12.83 mm, 12.84 mm, 12.85 mm, 12.86 mm, 12.87 mm, 12.88 mm, 12.89 mm, 12.9 mm, 12.91 mm, 12.92 mm, 12.93 mm, 12.94 mm, 12.95 mm, 12.96 mm, 12.97 mm, 12.98 mm, 12.99 mm, or 13 mm, and (iii) a height or thickness of approximately 5 mm, 5.01 mm, 5.02 mm, 5.03 mm, 5.04 mm, 5.05 mm, 5.06 mm, 5.07 mm, 5.08 mm, 5.09 mm, 5.1 mm, 5.11 mm, 5.12 mm, 5.13 mm, 5.14 mm, 5.15 mm, 5.16 mm, 5.17 mm, 5.18 mm, 5.19 mm, 5.2 mm, 5.21 mm, 5.22 mm, 5.23 mm, 5.24 mm, 5.25 mm, 5.26 mm, 5.27 mm, 5.28 mm, 5.29 mm, 5.3 mm, 5.31 mm, 5.32 mm, 5.33 mm, 5.34 mm, 5.35 mm, 5.36 mm, 5.37 mm, 5.38 mm, 5.39 mm, 5.4 mm, 5.41 mm, 5.42 mm, 5.43 mm, 5.44 mm, 5.45 mm, 5.46 mm, 5.47 mm, 5.48 mm, 5.49 mm, 5.5 mm, 5.51 mm, 5.52 mm, 5.53 mm, 5.54 mm, 5.55 mm, 5.56 mm, 5.57 mm, 5.58 mm, 5.59 mm, 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, 5.8 mm, 5.81 mm, 5.82 mm, 5.83 mm, 5.84 mm, 5.85 mm, 5.86 mm, 5.87 mm, 5.88 mm, 5.89 mm, 5.9 mm, 5.91 mm, 5.92 mm, 5.93 mm, 5.94 mm, 5.95 mm, 5.96 mm, 5.97 mm, 5.98 mm, 5.99 mm, or 6 mm. In yet another embodiment, the pharmaceutical composition may have (i) a length of approximately 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, or 19.3 mm as measured on the major axis, (ii) a width of approximately 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, or 12.5 mm, and (iii) a height or thickness of approximately 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, or 5.8 mm.

In additional embodiments, the pharmaceutical composition may expand upon immersion in fluid to have (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, or 21 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, or 14 mm within about 5 minutes of immersion in fluid. In other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, or 22 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1

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mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 10 minutes to about 15 minutes of immersion in fluid. In still other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, or 22.5 mm; and (ii) a width of about 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 20 minutes to about 25 minutes of immersion in fluid. In additional embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, or 23 mm; and (ii) a width of about 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 30 minutes to about 35 minutes of immersion in fluid. In still other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 18 mm, 18.1 mm, 18.2 mm, 18.3 mm, 18.4 mm, 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2 mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height or thickness of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 50 minutes to about 55 minutes of immersion in fluid. In yet another embodiment, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2

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mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height or thickness of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 60 minutes of immersion in fluid.

In yet another embodiment, the length of the pharmaceutical composition increases by about 4%, 4.25%, 4.5%, 4.75%, 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, or 13% within about 10 minutes of immersion in fluid. In still another embodiment, the length of the pharmaceutical composition increases by about 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 15 minutes of immersion in fluid. In yet another embodiment, the length of the pharmaceutical composition increases by about 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 20 minutes of immersion in fluid. In a further embodiment, the length of the pharmaceutical composition increases by about 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18% within about 30 minutes of immersion in fluid. In another embodiment, the length of the pharmaceutical composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, or 19% within about 45 minutes of immersion in fluid. In yet another embodiment, the length of the pharmaceutical composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, or 19% within about 55 minutes of immersion in fluid. In still another embodiment, the length of the pharmaceutical composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, or 20% within about 60 minutes of immersion in fluid.

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In a further embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 10 minutes of immersion in fluid. In still another embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 15 minutes of immersion in fluid. In yet another embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 20 minutes of immersion in fluid. In a further embodiment, the width of the pharmaceutical composition increases by about 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, or 24% within about 30 minutes of immersion in fluid. In another embodiment, the width of the pharmaceutical composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 45 minutes of immersion in fluid. In yet another embodiment, the width of the pharmaceutical composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 55 minutes of immersion in fluid. In still another embodiment, the width of the pharmaceutical composition increases by about 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, 25%, 25.25%, 25.5%, 25.75%, or 26% within about 60 minutes of immersion in fluid.

The pharmaceutical composition disclosed herein includes one or more dosage forms that are designed to achieve the therapeutic concentrations of the active ingredients. In some

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embodiments, therefore, a therapeutically effective dose of the pharmaceutical composition may comprise one dosage form. In other embodiments, a therapeutically effective dose of the pharmaceutical composition may comprise two dosage forms. In additional embodiments, a therapeutically effective dose of the pharmaceutical composition may comprise three or more dosage forms.

(d) Abuse and Tamper Resistant Properties of the Composition

Extended release pain medications have provided many benefits to patients in the management of their chronic pain by providing a sustained release over time of a larger quantity of drug than is typically contained in an immediate release formulation. Consequently, these dosage forms (especially if they contain opioids) are attractive targets for drug abusers looking to defeat the extended release formulation to allow immediate bolus administration or "dose-dumping" of the entire drug contents of the dosage form.

Dosage forms of the pharmaceutical composition disclosed herein may be more resistant to crushing, grinding, pulverizing, or other common means used to produce a powder than an immediate release product. Accordingly, some embodiment forms are tamper resistant and less prone to abuse or misuse. For example, certain embodiments may not be crushed into a powder and snorted. Additionally, some embodiments comprising an extended release polymer may not be crushed, mixed with an aqueous solution, and injected (i.e., the resultant mixture becomes extremely viscous and cannot be drawn into a syringe).

For example, dosage forms of the pharmaceutical composition disclosed herein form a pasty semi-solid mixture when dissolved. Thus, the pharmaceutical composition is difficult to draw into a syringe and inject intravenously. The yield of active pharmaceutical ingredient(s) obtained from the pharmaceutical composition is also low (less than 20%).

Further, dosage forms of the pharmaceutical composition disclosed herein cannot easily be snorted. In order for a drug abuser to successfully snort a drug obtained from a dosage form, he must prepare a crushed, finely divided powder form of the dosage form for insufflating the powder into the nasal cavity. However, the pharmaceutical compositions disclosed herein form a clumpy, solid mass and do not allow acceptable absorption through the nasal tissue.

Dosage forms of the pharmaceutical composition disclosed herein also do not allow "dose dumping" caused by the deliberate introduction of alcohol into a drug abuser's stomach which accelerates the release of active ingredient(s) from the time-release formulation. The pharmaceutical compositions disclosed herein are resistant to the accelerated release of active ingredient(s).

In addition, dosage forms of the pharmaceutical composition disclosed herein do not allow for "free basing." Successful free basing by a drug abuser requires the generation of a salt free form of the active pharmaceutical ingredient(s). This requires physical and chemical manipulation to release the active pharmaceutical ingredient(s) from its salt(s) and selective extraction from other matrix excipients. The pharmaceutical composition disclosed herein cannot be easily manipulated to generate a free base preparation.

Moreover, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the average molecular weight of the extended release polymer used in the pharmaceutical composition. In another embodiment, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the amount of the extended release polymer used in the pharmaceutical composition.

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In further embodiments, the solid oral dosage forms of the pharmaceutical compositions disclosed herein exhibit substantial differences in the release profiles of oxycodone and acetaminophen when the dosage forms are crushed or ground. Indeed, the intact solid oral dosage forms surprisingly exhibit a higher release rate of both active ingredients than one that is crushed or ground. This suggests that upon grinding or crushing the solid oral dosage forms disclosed herein, the immediate release portion and extended release portion of the dosage form combine, and the hydration and swelling of the polymer(s) in the extended release portion of the dosage form retards the release of the oxycodone and acetaminophen in the immediate release portion. Hence the incorporation of the ground or crushed components from the immediate release portion into a mixture with the ground or crushed components of the extended release portion causes the pharmaceutical composition to lose its immediate release characteristics. This feature may effectively negate a drug abuser's purpose for crushing the solid oral dosage form in the first place—to obtain an early onset of analgesia. Thus, this is an unexpected tamper resistant property of the pharmaceutical compositions disclosed herein.

In another embodiment, as the amount of oxycodone in the pharmaceutical composition increases, so does the duration of gastric retention after administration to a subject. Consequently, if a subject either intentionally or accidentally ingests a larger dose of the pharmaceutical composition than prescribed, the pharmaceutical composition will be retained in the stomach for a longer time period than an IR or traditional ER pharmaceutical composition, thereby giving a medical provider additional time to perform gastric lavage, induce vomiting, or administer activated charcoal to prevent the body from absorbing the oxycodone. In a further embodiment, the pharmaceutical composition provides a medical provider with about an additional 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 2.0 hours, 2.25 hours, 2.5 hours, 2.75 hours, 3.0 hours, 3.25 hours, 3.5 hours, 3.75 hours, or 4 hours in which to prevent the absorption of oxycodone in the subject. In another embodiment, the pharmaceutical composition provides a medical provider with sufficient time to treat a subject who has overdosed on oxycodone so that death, difficulty breathing, cardiac arrest, and limp muscles do not occur in the subject.

In yet another embodiment, if vomiting is induced or naturally occurs as a result of an increased dose of oxycodone, the entire pharmaceutical composition is expelled from the subject. Thus, toxic concentrations of the oxycodone due to absorption into the subject's blood are prevented by removing the further release of oxycodone. In still another embodiment, if vomiting is induced or naturally occurs as a result of the increased dose of oxycodone about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the pharmaceutical composition is expelled from the subject. In yet another embodiment, if vomiting is induced or naturally occurs within about 30 minutes to about 60 minutes after ingestion of the increased dose of oxycodone about 50% to about 65% of the oxycodone dose is expelled from the subject.

(e) In Vitro Release Properties of the Composition

The in vitro release rates of oxycodone and acetaminophen from the pharmaceutical compositions disclosed herein may be measured in 900 mL of 0.1 N HCl using a USP type II paddle apparatus and at a paddle speed of either about 100 rpm or 150 rpm and a constant temperature of 37° C.

In one embodiment, the at least one immediate release portion of the composition may have in vitro release rates of

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oxycodone and acetaminophen as follows: more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes, or essentially 100% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes. In another embodiment, more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 minutes. In yet another embodiment, essentially 100% of the oxycodone and/or acetaminophen present in the at least one immediate release portion may be released within about 5 minutes.

In one embodiment, the at least one extended release portion of the composition may have in vitro release rates of oxycodone as follows: from about 1% to about 20% of the oxycodone present in the at least one extended release portion may be released within about 15 minutes, from about 35% to about 55% of the oxycodone present in the at least one extended release portion may be released within about 2 hours, from about 65% to about 85% of the oxycodone present in the at least one extended release portion may be released within about 4 hours, and at least about 90% of the oxycodone present in the at least one extended release portion may be released within about 8 hours.

In yet another embodiment, the at least one extended release portion may have in vitro release rates of oxycodone as follows: from about 1% to about 10% of the oxycodone present in the at least one extended release portion may be released within about 15 minutes, from about 40% to about 50% of the oxycodone present in the at least one extended release portion may be released within about 2 hours, from about 70% to about 80% of the oxycodone present in the at least one extended release portion may be released within about 4 hours, and from about 90% to about 100% of the oxycodone present in the at least one extended release portion may be released within about 8 hours.

In one embodiment, the at least one extended release portion may have in vitro release rates of acetaminophen as follows: from about 1% to about 15% of the acetaminophen present in the at least one extended release portion may be released within about 15 minutes, from about 25% to about 40% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 50% to about 65% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 80% to about 95% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

In another embodiment, the at least one extended release portion of the composition may have in vitro release rates of acetaminophen as follows: from about 1% to about 5% of the acetaminophen present in the at least one extended release portion may be released within about 15 minutes, from about 25% to about 35% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 55% to about 65% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 80% to about 90% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

In one embodiment, the in vitro release rates of oxycodone from the composition may be as follows: about 25% to about 35% of oxycodone may be released from the composition within about 15 minutes, from about 50% to about 65% of oxycodone may be released from the composition in about 2 hours, from about 70% to about 85% of oxycodone may be

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released from the composition within about 4 hours, and from about 90% to about 100% of oxycodone may be released from the composition within about 8 hours.

In another embodiment, the pharmaceutical composition disclosed herein may have in vitro release rates of oxycodone as follows: about 25% to about 30% of oxycodone may be released from the pharmaceutical composition within about 15 minutes, from about 50% to about 60% of oxycodone may be released from the pharmaceutical composition within about 2 hours, from about 70% to about 80% of oxycodone may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 95% of oxycodone may be released from the pharmaceutical composition within about 8 hours.

In one embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: from about 50% to about 55% of acetaminophen may be released from the composition in about 15 minutes, from about 60% to about 75% of acetaminophen may be released from the composition in about 2 hours, from about 75% to about 85% of acetaminophen may be released from the composition in about 4 hours, and from about 90% to about 100% of acetaminophen may be released from the composition in about 8 hours.

In another embodiment, the in vitro release rates of acetaminophen from the pharmaceutical composition disclosed herein may be as follows: from about 50% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes, from about 60% to about 70% of acetaminophen may be released from the pharmaceutical composition within about 2 hours, from about 75% to about 85% of acetaminophen may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 100% of acetaminophen may be released from the pharmaceutical composition within about 8 hours.

Additionally, the in vitro release rates of oxycodone and acetaminophen from the pharmaceutical composition generally are not affected by low concentrations of ethanol (i.e., from about 5% v/v to about 20% v/v) when measured in 900 mL of 0.1 N HCl containing the desired percentage of ethanol using a USP type II paddle apparatus and at a paddle speed of about 150 rpm and a constant temperature of 37° C. For example, from about 25% to about 35% of oxycodone and about 50% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes when measured in the presence of 5% to 20% ethanol, and from about 50% to about 65% of oxycodone and from about 60% to about 70% of acetaminophen may be released from the pharmaceutical composition within about 2 hours when measured in the presence of 5% to 20% ethanol.

The in vitro release rates of oxycodone and acetaminophen from the pharmaceutical compositions disclosed herein generally are reduced, however, in the presence of 40% ethanol. For example, from about 5% to about 15% of the oxycodone and from about 15% to about 25% of the acetaminophen may be released from the pharmaceutical composition within about 15 minutes when measured in the presence of 40% ethanol, and from about 35% to about 45% of oxycodone and from about 45% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 2 hours when measured in the presence of 40% ethanol.

Stated another way, less oxycodone is extracted from the pharmaceutical composition by a solution of 0.1 N HCl and 40% ethanol than is extracted by a solution of 0.1 N HCl. In some embodiments, less than about 75% of the oxycodone that is released in the presence of 0.1N HCl may be released

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in the presence of 0.1N HCl containing 40% ethanol. In additional embodiments, less than about 70%, 65%, 60%, 55%, 50%, 45%, or 40% of the oxycodone that may be released in the presence of 0.1N HCl may be released in the presence of 0.1N HCl and 40% ethanol. For example, less than about 40% of the oxycodone that may be released in the presence of 0.1N HCl in about 15 minutes may be released in the presence of 0.1N HCl and 40% ethanol within about 15 minutes. In other embodiments, less than about 60% of the oxycodone that may be released in the presence of 0.1N HCl in about 30 minutes may be released in the presence of 0.1N HCl and 40% ethanol within about 30 minutes. In additional embodiments, less than about 75% of the oxycodone that may be released in the presence of 0.1N HCl in about 2 hours may be released in the presence of 0.1N HCl and 40% ethanol within about 2 hours.

(f) Stability Data for the Pharmaceutical Composition

In one embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in any amount up to and including, but no more than, about 100 ppm. In other embodiments, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.6 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In still another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm, 0.3 ppm, 0.4 ppm, 0.5 ppm, 0.6 ppm, 0.7 ppm, 0.8 ppm, 0.9 ppm, 1.0 ppm, 1.1 ppm, 1.2 ppm, 1.3 ppm, 1.4 ppm, 1.5 ppm, 1.6 ppm, 1.7 ppm, 1.8 ppm, 1.9 ppm, 2.0 ppm, 2.1 ppm, 2.2 ppm, 2.3 ppm, 2.4 ppm, 2.5 ppm, 2.6 ppm, 2.7 ppm, 2.8 ppm, 2.9 ppm, 3.0 ppm, 3.1 ppm, 3.2 ppm, 3.3 ppm, 3.4 ppm, 3.5 ppm, 3.6 ppm, 3.7 ppm, 3.8 ppm, 3.9 ppm, 4.0 ppm, 4.1 ppm, 4.2 ppm, 4.3 ppm, 4.4 ppm, 4.5 ppm, 4.6 ppm, 4.7 ppm, 4.8 ppm, 4.9 ppm, 5.0 ppm, 5.1 ppm, 5.2 ppm, 5.3 ppm, 5.4 ppm, 5.5 ppm, 5.6 ppm, 5.7 ppm, 5.8 ppm, 5.9 ppm, and 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in any amount up to and including about 0.5% by weight of the oxycodone. In other embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to 4° C. and at about 60% to 75% relative humidity. In yet another embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to 40° C. and at about 60% to 75% relative humidity. In additional embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%,

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0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, Related Substance A (i.e., C-Normorphinan-6-carboxylic acid, 4,5-epoxy-6,14-dihydroxy-3-methoxy-17-methyl-, (5 α ,6 α)-) may be present in the pharmaceutical composition as a degradation product of oxycodone in a maximum amount of about 0.5% by weight of the oxycodone. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet another embodiment, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition in any amount up to about 0.15% by weight of the acetaminophen. In another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In still another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.05% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In other embodiments, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, and 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in a maximum amount of about 0.2% by weight of the oxycodone. In other embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01% to about 0.2% by weight of the oxycodone after storage for about 1, 2,

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or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet another embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.05% to about 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In further embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, and 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, the total acetaminophen degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the acetaminophen. In other embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In further embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, the total oxycodone degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the oxycodone. In further embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet other embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

(g) In Vivo and Pharmacokinetic Properties of the Pharmaceutical Composition

The pharmaceutical composition disclosed herein comprises at least one immediate release portion for immediate release of oxycodone and acetaminophen such that therapeutic plasma concentrations are quickly attained (e.g., within one hour) and the initial onset of action is achieved within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition upon oral administration to a subject. The pharmaceutical composition disclosed herein also comprises at least one extended release portion for sustained release of oxycodone and acetaminophen over an extended period of time, e.g., about 3 to about 12 hours, or about 4 to about 9 hours, or at least about 6 hours, or at least about 8 hours, to the

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upper gastrointestinal tract where acetaminophen, and potentially oxycodone, is best absorbed.

The pharmaceutical composition may be orally administered to a subject once in a 24 hour period (q.d. or once-daily), two times in a 24 hour period (b.i.d. or twice-daily), or three times in a 24 hour period (t.i.d. or three times daily). In one embodiment, the pharmaceutical composition may be orally administered to the subject twice a day (i.e., every 12 hours). The subject may be a mammal, and in certain embodiments, the subject may be a human.

In another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition. This first or loading dose may assist the subject in more quickly attaining steady state blood levels of the active drugs. In a further embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising about 22.5 mg of oxycodone and about 975 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 tablets, each tablet comprising about 11.25 mg of oxycodone and about 462.5 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 tablets, each tablet comprising about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 tablets, each tablet comprising about 5.625 mg of oxycodone and about 231.25 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 capsules, each capsule comprising about 11.25 mg of oxycodone and about 462.5 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 capsules, each capsules comprising about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 capsules, each capsules comprising about 5.625 mg of oxycodone and about 231.25 mg of acetaminophen.

Upon oral administration to a subject, the pharmaceutical composition disclosed herein may maintain a therapeutic blood plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hours to about 12 hours after administration of the composition. In another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 1 hour to about 12 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 2 hour to about 10 hours after administration of the composition. In yet another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 1 hour to about 10 hours after administration of the composition. In still another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 0.75 hour to about 10 hours after administration of the composition.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} (peak plasma concen-

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tration) for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg. In another embodiment, the mean C_{max} for oxycodone may range from about 1.0 ng/mL/mg to about 1.5 ng/mL/mg. In an additional embodiment, the mean C_{max} for oxycodone may be 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, or 1.6 ng/mL/mg. Moreover, the mean C_{max} for oxycodone at steady state may range from about 1.5 ng/mL/mg to about 2.0 ng/mL/mg, from about 1.6 ng/mL/mg to about 1.95 ng/mL/mg, or from about 1.7 ng/mL/mg to about 1.85 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of oxycodone. Deconvolution of the pharmaceutical composition and the target plasma profiles can be done in WinNonLin (version 5.2, Pharsight Corp., Mountain View, Calif.). The results of such a deconvolution analysis for oxycodone is depicted in FIG. 23. The biphasic absorption of oxycodone may be characterized by an initial rapid absorption resulting in a first peak in plasma concentration between about 1 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours as a result of slower absorption taking place from the at least one extended release portion after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic increase in blood plasma concentrations of oxycodone may be characterized by a plasma concentration-time profile for oxycodone in which the slope of a line drawn between 0 hour and about 2 hours is greater than the slope of a line drawn between about 2 hours and about 5 hours. See FIG. 23.

This biphasic increase in oxycodone levels resulting from the composition has several benefits. For example, providing rapid but not too high concentrations of oxycodone for quick onset of analgesia followed by maintenance of oxycodone levels over an extended time period could prevent a human subject from developing liking or dependence (abuse) for oxycodone. Further fluctuations in the oxycodone plasma levels could also prevent development of tolerance at the active site. Thus, the biphasic increase in oxycodone levels helps to prevent this acute tolerance.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for oxycodone from about 9.0 ng·hr/mL/mg to about 18.5 ng·hr/mL/mg. In a further embodiment, the mean AUC for oxycodone may be from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg. In another embodiment, the mean AUC for oxycodone may be about 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, or 16.0 ng·hr/mL/mg. Additionally, the mean AUC for oxycodone at steady state may range from about 11.0 ng·hr/mL/mg to about 17.0 ng·hr/mL/mg, from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} (time to peak plasma concentration) for oxycodone from about 2.0 hours to about 7.0 hours. In an alternate embodiment, the median T_{max} for oxycodone may be from about 3.0 hours to about 6.0 hours. In another embodiment, the median T_{max} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 or 6.0 hours. Moreover, the median T_{max} for oxycodone at steady state may range from about 1.5 hours to about 3.5 hours, or from about 2 hours to about 3 hours.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median tlag for oxycodone from about 0 hours to about 0.5 hours. In an alternate embodiment, the median tlag for oxycodone may be from about 0 hours to about 0.25 hours.

Rates of absorption are often assessed by comparing standard pharmacokinetic parameters such as T_{max} and C_{max} . The extent of absorption is assessed by the AUC. A short T_{max} has been used to indicate rapid absorption. The U.S. FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (March 2003) and related publications (Chen et al, Clin. Pharmacokinet. 40 (8):565-72, 2001) also recommends the use of partial AUC for some modified-release drugs ("MR drugs"), such as the pharmaceutical compositions disclosed herein. A partial AUC calculation may be used to measure early exposure to a drug, which may signify an initial onset of pain relief and/or to measure prolonged exposure of a drug in achieving sustained relief. Partial AUC calculations can also demonstrate whether two MR drugs are truly bioequivalent by comparing, for example, an early partial AUC, which will be associated with a drug's response onset, and a late partial AUC, which will be associated with a drug's sustained response. The parameters for compositions vary greatly between subjects. The parameters also vary depending on aspects of the study protocol such as the sampling scheduling, subject posture and general subject health. Values quoted in this specification are given as mean±standard deviation unless otherwise noted.

For partial AUC calculations, the standard linear trapezoidal summation over each time interval is used. The partial AUCs are calculated from the mean pharmacokinetic profile. For time 0 to 1 hour the partial AUC is $AUC_{(0-1hr)}$; for time 0 to 2 hours the partial AUC is $AUC_{(0-2hr)}$; for time 0-4 hours the partial AUC is $AUC_{(0-4hr)}$; for time 0 to 6 hour the partial AUC is $AUC_{(0-6hr)}$; for time 0 to 8 hours the partial AUC is $AUC_{(0-8hr)}$; and for time 0 to the last measurable time point ("x") the partial AUC is $AUC_{(0-(x)hr)}$ where each partial AUC is calculated according to standard pharmaceutical industry pharmacokinetic calculation methodologies as given by:

AUC_(0-1 hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 1 hour.

AUC_(0-2hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 2 hours.

AUC_(0-4hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 4 hours.

AUC_(0-6hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 6 hours.

AUC_(0-8hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 8 hours.

AUC_{(0-t)hr}—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the last measurable time point.

AUC_{(0-(T_{max} of IR product+2SD))}—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations ("2SD") for the immediate release drug. The FDA has identified this calculation in association with an early onset of response for certain modified-release dosage forms, which show complex pharmacokinetic characteristics.

(See *supra* March 2003 Guidance; Draft Guidance on Dexamethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (November 2011)).

$AUC_{((T_{max} \text{ of IR product} + 2SD) - t)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations (“2SD”) for the immediate release drug to the last measurable time point. The FDA has identified this parameter in association with sustaining the response for modified-release dosage forms, which shows complex pharmacokinetic characteristics. (See March 2003 Guidance *supra*; Draft Guidance on Dexmethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (November 2011)).

AUC_{(x-y)hr}—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time “x” (e.g., any measurable time point, such as 8 hours) to time “y” (e.g., any other measurable time point later than “x”, such as 12 hours).

AUC_(0-∞)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time 0 to infinity.

Further, partial AUC may be calculated using trapezoidal summation from time Tmax to time t (the last measured time point of plasma concentration profile).

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for oxycodone from about 0.10 ng-hr/mL/mg to about 0.45 ng-hr/mL/mg, from about 0.15 ng-hr/mL/mg to about 0.25 ng-hr/mL/mg, or from about 0.25 ng-hr/mL/mg to about 0.35 ng-hr/mL/mg. In another embodiment, the AUC_{0-1hr} for oxycodone may be about 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, or 0.45 ng-hr/mL/mg.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.65 ng·hr/mL/mg to about 1.35 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be about 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30 or 1.35 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for oxycodone from about 2.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, from about 2.5 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, or 4.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{T_{max-t}}$ for oxycodone from about 5.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, from about 8.0 ng·hr/mL/mg to about 10.5 ng·hr/mL/mg, or from about 10.5 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg. In another embodiment, the $AUC_{T_{max-t}}$ for oxycodone may be about 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0 or 16.0 ng·hr/mL/mg.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-T_{max} \text{ of IR product} + 2SD)}$ for oxycodone after a single dose from about 1.0 ng-hr/mL/mg to about 3.0 ng-hr/mL/mg, from about 1.50 ng-hr/mL/mg to about 2.5 ng-hr/mL/mg, or from about 1.75 ng-hr/mL/mg

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mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$:

oxycodone mean±SD=1.0 h±0.89 h; T_{max}+2SD=2.8 hours

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-2.8)}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-2.8)}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(2.8-48)}$ for oxycodone after a single dose from about 7.5 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, from about 8.45 ng·hr/mL/mg to about 13.7 ng·hr/mL/mg, or from about 9.5 ng·hr/mL/mg to about 11.5 ng·hr/mL/mg. In another embodiment, the $AUC_{(2.8-48)}$ for oxycodone may be about 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, or 12.5 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$:

oxycodone mean±SD=1.9 h±1.2 h; T_{max}+2SD=4.3 hours

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-4.3)}$ for oxycodone after a single dose from about 1.5 ng·hr/mL/mg to about 5.5 ng·hr/mL/mg, from about 2.0 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, from about 2.5 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-4.3)}$ for oxycodone may be about 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, 3.5, 3.55, 3.6, 3.65, 3.7, 3.75, 3.8, 3.85, 3.9, 3.95, 4.0, 4.05, 4.1, 4.15, 4.2, 4.25, 4.3, 4.35, 4.4, 4.45, 4.5, 4.55, 4.6, 4.65, 4.7, 4.75, 4.8, 4.85, 4.9, 4.95, 5.0, 5.05, 5.1, 5.15, 5.2, 5.25, 5.3, 5.35, 5.4, 5.45, or 5.5 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(4.3-48)}$ for oxycodone after a single dose from about 5.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 13.5 ng·hr/mL/mg, from about 9.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 9.5 ng·hr/mL/mg to about 11.5 ng·hr/mL/mg. In another embodiment, the $AUC_{(4.3-48)}$ for oxycodone may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5,

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8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject in a fasted state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 3% to about 33% of the AUC_{0-r} , from about 10% to about 27% of the AUC_{0-r} , or from about 15% to about 22% of the AUC_{0-r} . In another embodiment, the pharmaceutical composition, when orally administered to a subject in a fed state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 5% to about 35% of the AUC_{0-r} , from about 12% to about 30% of the AUC_{0-r} , or from about 15% to about 25% of the AUC_{0-r} .

In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may provide a mean half-life of oxycodone that ranges from about 3.5 hours to about 5.5 hours, or from about 4 hours to about 5 hours. In various embodiments, the mean half-life of oxycodone may be about 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, or 5.2 hours.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, produces a plasma profile characterized by an abuse quotient for oxycodone from about 3 to about 5. In other embodiments, the abuse quotient for oxycodone may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0.

Moreover, upon oral administration, the pharmaceutical composition disclosed herein may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 1 hour to about 6 hours after administration. In another embodiment, the pharmaceutical composition may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 0.75 hour to about 6.5 hours after administration. In yet another embodiment, the composition may maintain a plasma concentration of acetaminophen of at least about 1 mg/mL from about 0.5 hour to about 12 hours after administration.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg. In other embodiments, the mean C_{max} for acetaminophen may be from about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, or 11.0 ng/mL/mg. Moreover, the mean C_{max} for acetaminophen at steady state may range from about 6.0 ng/mL/mg to about 9.0 ng/mL/mg, from about 6.5 ng/mL/mg to about 8.5 ng/mL/mg, or from about 7.0 ng/mL/mg to about 8.0 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of acetaminophen. The biphasic absorption of acetaminophen may be characterized by an initial rapid absorption resulting in first peak in plasma concentrations between about 0.5 hour and 2 hours, which contributes to the early onset on action, and a second peak in plasma concentrations between about 3 hours and 7 hours after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic increase in blood plasma concentrations of acetaminophen is characterized by a plasma concentration-time profile for acetaminophen in

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which the slope of a line drawn between 0 hour and 2 hour is greater than the slope of a line drawn between about 2 hours and 5 hours. See FIG. 24.

This biphasic increase in acetaminophen levels resulting from the composition has several benefits. For example, the initial rapid rise in plasma levels produce quick onset of analgesia and the slower absorption provides maintenance of analgesia for an extended period of time.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for acetaminophen from about 35.0 ng·hr/mL/mg to about 80.0 ng·hr/mL/mg. In a further embodiment, the mean AUC for acetaminophen may range from about 35.0 ng·hr/mL/mg to about 60.0 ng·hr/mL/mg. In other embodiments, the mean AUC for acetaminophen may be about 35.0, 40.0, 45.0, 50.0, 55.0, 60.0, 65.0, 70.0, 75.0, or 80.0 ng·hr/mL/mg. Additionally, the mean AUC for acetaminophen at steady state may range from about 40.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg, from about 35.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 37.0 ng·hr/mL/mg to about 42.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} for acetaminophen from about 0.5 hours to about 6.0 hours. In another embodiment, the median T_{max} for acetaminophen may be from about 1.0 hour to about 5.0 hours. In a further embodiment, the median T_{max} for acetaminophen may range from about 0.5 hour to about 4.0 hours. In still another embodiment, the median T_{max} for acetaminophen may range from about 0.75 to about 1.5 hours. In other embodiments, the median T_{max} may be about 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 hours. Moreover, the median T_{max} for acetaminophen at steady state may range from about 0.5 hour to about 1.0 hour, or from about 0.5 hour to about 0.75 hour.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median tlag for acetaminophen from about 0 hour to about 0.5 hour. In an alternate embodiment, the median tlag for acetaminophen may be from about 0 hour to about 0.25 hour. In one embodiment, the median tlag for acetaminophen may be 0 hour. In another embodiment, the median tlag for acetaminophen may be 0.25 hour.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by various partial AUCs for acetaminophen. The partial AUCs for acetaminophen are calculated as described above for oxycodone. The pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for acetaminophen from about 1.25 ng·hr/mL/mg to about 3.25 ng·hr/mL/mg, from about 1.60 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 2.75 ng·hr/mL/mg. In another embodiment, the AUC_{0-1hr} for acetaminophen may be about 1.25, 1.30, 1.40, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, 2.30, 2.35, 2.40, 2.45, 2.50, 2.55, 2.60, 2.65, 2.70, 2.75, 2.80, 2.85, or 2.90 ng·hr/mL/mg.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 4.25 ng·hr/mL/mg to about 8.75 ng·hr/mL/mg, from about 5.50 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 6.0 ng·hr/mL/mg to about 7.25 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen

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may be about 4.25, 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.50, 7.75 or 8.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for acetaminophen from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, from about 13.0 ng·hr/mL/mg to about 14.5 ng·hr/mL/mg, or from about 14.5 ng·hr/mL/mg to about 16.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for acetaminophen may be about 10.0, 11.0, 12.0, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, or 17.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{Tmax-t} for acetaminophen from about 20.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg, from about 23.5 ng·hr/mL/mg to about 36.0 ng·hr/mL/mg, or from about 29.0 ng·hr/mL/mg to about 31.0 ng·hr/mL/mg. In another embodiment, the AUC_{Tmax-t} for acetaminophen may be about 20.0, 21.0, 22.0, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5 or 36.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$ for acetaminophen may be about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$:

$$\text{acetaminophen mean} \pm \text{SD} = 0.596 \text{ h} \pm 0.529 \text{ h; } T_{max} + 2SD = 1.65 \text{ hour}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-1.7)}$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-1.7)}$ for acetaminophen may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(1.7-4.8)}$ for acetaminophen after a single dose from about 25.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 31.5 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(1.7-4.8)}$ for acetaminophen may be about 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0,

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37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$:

$$\text{acetaminophen mean} \pm SD = 1.48 \text{ h} \pm 0.875 \text{ h; } T_{max} + 2SD = 3.2 \text{ hour}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3.2)}$ for acetaminophen after a single dose from about 7.0 ng·hr/mL/mg to about 21.0 ng·hr/mL/mg, from about 9.0 ng·hr/mL/mg to about 18.0 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-3.2)}$ for acetaminophen may be about 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, or 21.0 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3.2-48)}$ for acetaminophen after a single dose from about 15.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, from about 27.5 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 30.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(3.2-48)}$ for acetaminophen may be about 15.0, 15.5, 16.0, 16.5, 17.0, 17.5, 18.0, 18.5, 19.0, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, 55.0, 55.5, 56.0, 56.5, 57.0, 57.5, 58.0, 58.5, 59.0, 59.5, 60.0, 60.5, 61.0, 61.5, 62.0, 62.5, 63.0, 63.5, 64.0, 64.5, 65.0, 65.5, 66.0, 66.5, 67.0, 67.5, 68.0, 68.5, 69.0, 69.5, 70.0, 70.5, 71.0, 71.5, 72.0, 72.5, 73.0, 73.5, 74.0, 74.5, or 75.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0 ng·hr/mL/mg to about 60.0 ng·hr/mL/mg, from about 30 ng·hr/mL/mg to about 50 ng·hr/mL/mg, from about 35 to about 45 ng·hr/mL/mg, or from about 37.5 ng·hr/mL/mg to about 42.5 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5,

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49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0. In a further embodiment, at AUC_{0-12hr} between about 70%-95%, about 75%-92%, or about 77%-90% of the acetaminophen has been cleared. In still another embodiment, about 80% of the acetaminophen has been cleared.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 30.0 to about 40.0 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15, 16, 17, 18, 19, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, or 50.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 5.0 ng·hr/mL/mg to about 25.0 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, or from about 10.0 ng·hr/mL/mg to about 15.0. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5 ng·hr/mL/mg to about 15.5 ng·hr/mL/mg, from about 2 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg, from about 3.5 ng·hr/mL/mg to about 10 ng·hr/mL/mg, or from about 4.5 ng·hr/mL/mg to about 6.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for acetaminophen from about 5 ng·hr/mL/mg to about 30 ng·hr/mL/mg, from about 10 ng·hr/mL/mg to about 20 ng·hr/mL/mg, or from about 13 ng·hr/mL/mg to about 17 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for acetaminophen from about 5.0, 6.0, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6,

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9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, or 20.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3-36hr)}$ for acetaminophen from about 20 ng·hr/mL/mg to about 50 ng·hr/mL/mg, from about 20 ng·hr/mL/mg to about 40 ng·hr/mL/mg, or from about 25 ng·hr/mL/mg to about 35 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3-36hr)}$ for acetaminophen from about 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5, or 50 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 50% to about 90% of the AUC_{0-r} , from about 55% to about 85% of the AUC_{0-r} , or from about 75% to about 85% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen that is about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84% or 85% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 40% to about 90% of the AUC_{0-r} , from about 55% to about 85% of the AUC_{0-r} , or from about 60% to about 75% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen of about 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 10% to about 40% of the AUC_{0-r} , from about 15% to about 35% of the AUC_{0-r} , or from about 20% to about 30% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen of about 10%, 12%, 14%, 16%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 5% to about 30% of the AUC_{0-r} , from about 7% to about 25% of the AUC_{0-r} , or from about 10% to about 20% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetami-

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nophen of about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of the AUC_{0-r} .

In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 3 hours to about 5 hours. In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 4 hours to about 5 hours. In various embodiments, the mean half-life of acetaminophen may be about 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, or 8 hours. In additional embodiments, the pharmaceutical composition, when orally administered to a subject, has a mean observed half-life of acetaminophen that is more than the mean half-life of commercially available immediate release acetaminophen products.

In another embodiment, upon administration of the pharmaceutical composition to a subject, the composition may provide at least about 4 hours to about 12 hours of drug delivery to the upper gastrointestinal tract, which includes the duodenum, jejunum, and ileum of the small intestine. In another embodiment, the composition may provide at least about 6 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 8 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 9 hours, or at least about 10 hours of drug delivery to the upper gastrointestinal tract.

In yet another embodiment, upon administration of the pharmaceutical composition to a subject, APAP undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to pre-systemic metabolism is referred to as the fraction absorbed and denoted "F_{ab}." This is different from the fraction bioavailable "F," which is the fraction that reaches the systemic circulation after the metabolism in the gut and liver.

In another embodiment, 60-90% of the acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 60-85% of acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See FIG. 27. Greater than 50% absorption of acetaminophen in the upper gastrointestinal tract is beneficial to a human subject because acetaminophen is poorly absorbed in the stomach and well absorbed in the small intestine and particularly, the upper segment of the gastrointestinal tract. It is therefore critical that acetaminophen is available in upper small intestine for its absorption. In one embodiment acetaminophen is released in stomach and reaches quickly into upper part of the small intestine for the absorption to take place.

In another embodiment, when about 60% to about 75% of the acetaminophen is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 27), about 15% to about 20% is

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absorbed in the distal jejunum (noted as “jejunum 2” in FIG. 27), and about 5% to about 15% is absorbed in the ileum.

In another embodiment, when about 70% to about 90% of the acetaminophen is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as “jejunum 1” in FIG. 27), about 15% to about 20% is absorbed in the distal jejunum (noted as “jejunum 2” in FIG. 27), and about 5% to about 15% is absorbed in the ileum.

In yet another embodiment, when at least about 55% of the total amount of the acetaminophen is released from the dosage form in the stomach within 1 hour after oral administration and when at least about 60% of the acetaminophen is released in the stomach after 2 hours, about 15% to about 20% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 30% to about 37% is absorbed in the proximal jejunum, about 15% to about 18% is absorbed in the distal jejunum, and about 8% to about 10% is absorbed in the ileum.

In still another embodiment, upon administration of the pharmaceutical composition to a subject, the opioid undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to presystemic metabolism is referred to as the fraction absorbed and denoted “*F_a*.” In one embodiment, the opioid is oxycodone. This is different from the fraction bioavailable “*F_b*,” which is the fraction that reaches the systemic circulation after metabolism in the gut and liver.

In a further embodiment, 70-95% of the oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 80-95% of oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See FIG. 28.

In one embodiment, the composition releases the opioid and other API in the stomach to optimize drug absorption in the duodenum and jejunum. For example, when about 25% to about 50% of oxycodone is released from the dosage form in the stomach within 1 hour following oral administration, about 10% to about 45% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 50% is absorbed in the proximal jejunum (noted as “jejunum 1” in FIG. 28), about 7% to about 20% is absorbed in the distal jejunum (noted as “jejunum 2” in FIG. 28), and about 2% to about 15% is absorbed in the ileum.

In another embodiment, when about 45% to about 65% of oxycodone is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 50% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 55% is absorbed in the proximal jejunum (noted as “jejunum 1” in FIG. 28), about 5% to about 25% is absorbed in the distal jejunum (noted as “jejunum 2” in FIG. 28), and about 2% to about 15% is absorbed in the ileum.

In another embodiment, when about 60% to about 85% of oxycodone is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 55% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic

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circulation, is absorbed in the duodenum, about 30% to about 60% is absorbed in the proximal jejunum (noted as “jejunum 1” in FIG. 28), about 10% to about 30% is absorbed in the distal jejunum (noted as “jejunum 2” in FIG. 28), and about 2% to about 20% is absorbed in the ileum.

In yet another embodiment, when at least 25% of the total amount of the oxycodone is released from the dosage form in the stomach within 1 hour after oral administration and when at least 45% of the oxycodone is released in the stomach after 2 hours, about 30% to about 45% of the total amount of oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 37% to about 43% is absorbed in the proximal jejunum (noted as “jejunum 1” in FIG. 28), about 10% to about 15% is absorbed in the distal jejunum (noted as “jejunum 2” in FIG. 28), and about 2% to about 8% is absorbed in the ileum.

In another embodiment, about 90% to about 100% of the IR dose of acetaminophen is released within about 15 minutes, 30 minutes, 45 minutes or 60 minutes after oral administration. In one embodiment, the dosage form provides a dissolution profile wherein about 20% to about 65%, about 35% to about 55% or about 40% to about 50% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration. In one embodiment, not more than 50% of the ER dose of acetaminophen is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the ER dose of acetaminophen is released within about the first hour. In another embodiment, not more than 85% of the ER dose of acetaminophen is released within about 4 hours. In yet another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 60% is released after about 6 hours. In one embodiment, the ER dose of acetaminophen is released over a time period of about 6 to 12, about 8 to 10, or about 9 to 10 hours in vitro. In another embodiment, the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In another embodiment, at least 90% or 95% of the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro.

In one embodiment, the pharmaceutical compositions disclosed herein rapidly achieve therapeutic plasma drug levels of oxycodone and acetaminophen similar to an immediate release product, which provides an early onset of action within about the first 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes or 60 minutes after administration of the composition, but unlike an immediate release product, the pharmaceutical composition is able to maintain those therapeutic plasma drug levels of oxycodone and acetaminophen over an extended period of time (e.g., up to 12 hours). Currently, there is no pharmaceutical composition available comprising oxycodone and acetaminophen which is able to provide a patient with quick onset of analgesia and maintenance of analgesia for an extended period of time.

In yet another embodiment, upon average, within one hour of administration to a subject, the pharmaceutical composition achieves a *C_{max}* for acetaminophen. The *C_{max}* achieved by the pharmaceutical composition disclosed herein is comparable to the *C_{max}* obtained from a commercially-available immediate release product containing acetaminophen formulated at half the strength of the commercially-available immediate release product. The acetaminophen continues to be released from the pharmaceutical composition at a rate less than the clearance rate for the acetaminophen, so that the

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acetaminophen levels fall smoothly until all of the acetaminophen is absorbed. Stated another way, the acetaminophen released by the pharmaceutical composition is eliminated by the body faster than it is being absorbed. The absorption of the acetaminophen released from the pharmaceutical composition is complete in about 8 to about 10 hours so that for one half life of acetaminophen the blood supply reaching the subject's liver via the portal vein contains no additional amounts of acetaminophen beyond the amounts present in the subject's general circulation.

These additional amounts of acetaminophen delivered to the liver from the subject's portal vein are frequently caused by the absorption of acetaminophen in the subject's gastrointestinal tract. Indeed, blood from the subject's intestines passes through the liver and then on to the general circulation. When acetaminophen is undergoing absorption, blood containing acetaminophen from the absorption process passes through the subject's liver prior to entering the general circulation where the acetaminophen is diluted by the distribution and clearance processes. The metabolism of these higher acetaminophen concentrations in blood coming into the subject's liver is termed the "first pass effect." Hence, the absorption process for acetaminophen taxes a subject's metabolic systems in the liver due to these higher "first pass" concentrations. Once the absorption process is complete, the concentration of acetaminophen in the blood reaching the subject's liver through the portal vein will be the same concentration of acetaminophen as found in blood throughout the rest of the subject's body. Thus, the pharmaceutical compositions disclosed herein provide a C_{max} comparable to a commercially-available immediate-release acetaminophen product (dosed at half strength) while providing a less taxing burden on the subject's metabolic systems in the liver because the acetaminophen released by the pharmaceutical composition is eliminated by the subject's body faster than it is being absorbed. This results in decreased levels of acetaminophen in a subject's liver as compared to an immediate release dosage form of acetaminophen dosed every 6 hours.

(h) Exemplary Compositions

In one embodiment, the pharmaceutical composition for extended release of oxycodone and acetaminophen comprises at least one extended release portion comprising acetaminophen, oxycodone or a combination thereof, and at least one extended release component; and at least one immediate release portion comprising oxycodone, acetaminophen or combinations thereof. In yet another embodiment, the pharmaceutical composition comprises an immediate release portion comprising oxycodone and acetaminophen and an extended release portion comprising oxycodone, acetaminophen and an extended release component. In still yet another embodiment, the composition comprises two extended release portions, each comprising an extended release component and one of the oxycodone or the acetaminophen, and an immediate release portion comprising the oxycodone and the acetaminophen. In another embodiment, the composition comprises two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and two immediate release portions, each comprising one of oxycodone or acetaminophen. In one embodiment, the extended release component comprises at least one extended release polymer. In another one embodiment, the extended release polymer comprises a polyethylene oxide. The molecular weight of the polyethylene oxide may be from about 500,000 Daltons to about 10,000,000 Daltons.

In another embodiment, the pharmaceutical composition may comprise from about 5 mg to about 30 mg of oxycodone

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and from about 250 mg to about 1300 mg of acetaminophen. In one exemplary embodiment, the pharmaceutical composition may comprise about 15 mg of oxycodone and about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 15 mg of oxycodone and about 500 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 15 mg of oxycodone and about 325 mg of acetaminophen. In a further embodiment, the composition may comprise about 30 mg of oxycodone and about 500 mg of acetaminophen. In yet another exemplary embodiment, the pharmaceutical composition may comprise about 7.5 mg of oxycodone about 325 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of oxycodone about 325 mg of acetaminophen. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of oxycodone about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 30 mg of oxycodone and about 650 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 22.5 mg of oxycodone and about 925 mg of acetaminophen.

In a further embodiment, a single dosage form of the pharmaceutical composition disclosed herein (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as either two dosage forms (e.g., two tablets) of the composition formulated at half the strength, or three dosage forms (e.g., three tablets) of the composition formulated at a third of the strength. In yet another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen). In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 5 mg of oxycodone and about 216.7 mg of acetaminophen). In yet another embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet comprising 22.5 mg of oxycodone and 650 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet configuration totaling 30 mg of oxycodone and 650 mg of acetaminophen. In yet a further exemplary embodiment, a pharmaceutical composition comprising 21 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet

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comprising 10.5 mg of oxycodone and 325 mg of acetaminophen). In yet another exemplary embodiment, a pharmaceutical composition comprising 22.5 mg of oxycodone and 925 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen).

In yet another embodiment, the at least one extended release portion of the composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen in the composition and from about 70% to about 80% (w/w) of the total amount of oxycodone in the composition, whereas the at least one immediate release portion may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen in the composition and from about 20% to about 30% (w/w) of the total amount of oxycodone in the composition. In still another embodiment, the at least one extended release portion may comprise about 50% (w/w) of the total amount of acetaminophen in the composition and about 75% (w/w) of the total amount of oxycodone in the composition; and the at least one immediate release portion may comprise about 50% (w/w) of total amount of acetaminophen in the composition and about 25% (w/w) of the total amount of oxycodone in the composition.

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In another embodiment, an extended release portion of the composition may comprise, by weight of such extended release portion, from about 30% to about 50% of the extended release polymer, from about 20% to about 40% of acetaminophen, and from about 0.5% to about 2% of oxycodone; and an immediate release portion may comprise, by weight of such immediate release portion, from about 70% to about 80% acetaminophen and from about 0.5% to about 1% of oxycodone.

In yet another embodiment, the pharmaceutical composition may comprise from about 7.5 mg to about 30 mg of oxycodone and from about 325 mg to about 650 mg of acetaminophen, wherein the at least one immediate release portion may comprise about 25% (w/w) of the total amount of oxycodone in the composition and about 50% (w/w) of the total amount of acetaminophen in the composition, and the at least one extended release portion may comprise about 75% (w/w) of the total amount of oxycodone in the composition, about 50% (w/w) of the total amount of acetaminophen in the composition, and about 35% to about 45%, by weight of the at least one extended release portion, of an extended release polymer comprising a polyethylene oxide.

Other exemplary formulations are set forth in Charts 1-2 below:

CHART 1

		Representative Oxycodone/Acetaminophen Formulations.									
		Formulation No.									
		1	2	3	4	5	6	7	8	9	10
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
Extended Release Layer	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N12K	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 1105	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3

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CHART 1-continued

		Representative Oxycodone/Acetaminophen Formulations.									
		Formulation No.									
		11	12	13	14	15	16	17	18	19	20
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	Anhydrous EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	Anhydrous EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N12K	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox 1105	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
		Formulation No.									
		21	22	23	24	25	26	27	28	29	30
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	Anhydrous EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
Extended Release Layer	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85

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CHART 1-continued

Representative Oxycodone/Acetaminophen Formulations.											
	Citric Acid	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	Anhydrous										
	EDTA disodium	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	salt, dihydrate										
	Hydroxypropyl	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	cellulose										
	Polyox N60K	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 205	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	methyl cellulose										
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
	Stearate										
Formulation No.											
		31	32	33	34	35	36	37	38	39	40
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	hydrochloride										
	Microcrystalline	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	cellulose										
	Pregelatinized	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	starch										
	Citric Acid	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	Anhydrous										
	EDTA disodium	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	salt, dihydrate										
	Hydroxypropyl	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	cellulose										
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
Extended Release Layer	Hydroxypropyl	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	methyl cellulose										
	Croscarmellose	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	sodium										
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
	stearate										
	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	hydrochloride										
	Microcrystalline	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	cellulose										
	Pregelatinized	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	starch										
	Citric Acid	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	Anhydrous										
	EDTA disodium	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	salt, dihydrate										
	Hydroxypropyl	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	cellulose										
	Polyox N60K	—	45.5	249.9	24.3	282.0	49.8	200.1	240.1	186.8	—
	Polyox 205	268.4	—	53.6	70.2	—	—	36.3	10.4	—	259.3
	Hydroxypropyl	—	90.5	—	65.4	—	192.1	—	—	127.3	142.0
	methyl cellulose										
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
	Stearate										
Formulation No.											
		41	42	43	44	45	46	47	48	49	50
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	hydrochloride										
	Microcrystalline	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	cellulose										
	Pregelatinized	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	starch										
	Citric Acid	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	Anhydrous										
	EDTA disodium	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	salt, dihydrate										
	Hydroxypropyl	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	cellulose										
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5

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CHART 1-continued

Representative Oxycodone/Acetaminophen Formulations.											
Extended Release Layer	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	Anhydrous EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N-750	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 301	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		51	52	53	54	55	56	57	58	59	60
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	Anhydrous EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	Anhydrous EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N-750	63.4	30.1	125.9	100.3	149.2	63.2	150.5	140.3	94.3	—
	Polyox 301	210.4	—	175.8	60.7	175.8	—	160.5	149.7	100.8	194.6
	Hydroxypropyl methyl cellulose	—	128.3	—	65.4	—	227.7	—	—	127.3	142.0
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2

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CHART 2

		Additional Oxycodone/Acetaminophen Formulations.									
		61	62	63	64	65	66	67	68	69	70
Immediate	APAP	250.0	250.0	250.0	250.0	250.0	250.0	325.0	325.0	162.5	162.5
Release	Oxycodone hydrochloride	3.75	3.75	3.75	7.5	7.5	7.5	3.75	3.75	2.5	3.75
Layer	Microcrystalline cellulose	23.72	23.72	23.72	32.42	32.42	32.42	28.10	28.10	15.50	18.40
	Pregelatinized starch	0.50	0.50	0.50	1.00	1.00	1.00	0.50	0.50	0.33	0.50
	Citric Acid Anhydrous	0.25	0.25	0.25	0.50	0.50	0.50	0.25	0.25	0.17	0.25
	EDTA disodium salt, dihydrate	0.05	0.05	0.05	0.10	0.10	0.10	0.05	0.05	0.033	0.05
	Hydroxypropyl cellulose	25.23	25.23	25.23	26.43	26.43	26.43	32.24	32.23	16.32	16.72
	Croscarmellose sodium	19.21	19.21	19.21	20.13	20.13	20.13	12.09	25.087	12.70	13.01
	Silicon dioxide	1.63	1.63	1.63	1.70	1.70	1.70	2.09	2.09	1.06	1.08
	Magnesium stearate	0.81	0.81	0.81	0.85	0.85	0.85	1.045	1.045	0.53	0.54
Extended	APAP	250.0	250.0	250.0	250.0	250.0	250.0	325.0	325.0	162.5	162.5
Release	Oxycodone hydrochloride	11.25	11.25	11.25	22.5	22.5	22.5	11.25	11.25	7.5	11.25
Layer	Microcrystalline cellulose	175.24	103.74	103.74	159.62	88.12	88.12	23.85	23.85	201.02	195.80
	Pregelatinized starch	1.50	1.50	1.50	3.00	3.00	3.00	1.50	1.50	1.00	1.50
	Citric Acid Anhydrous	0.75	0.75	0.75	1.50	1.50	1.50	0.75	0.75	0.50	0.75
	EDTA disodium salt, dihydrate	0.15	0.15	0.15	0.30	0.30	0.30	0.15	0.15	0.10	0.15
	Hydroxypropyl cellulose	15.13	15.13	15.13	17.11	17.11	17.11	—	19.16	9.91	10.57
	Polyox 1105	250.25	321.75	—	250.25	321.75	—	321.02	321.02	321.75	321.75
	Polyox N60K	—	—	321.75	—	—	321.75	—	—	—	—
	Silicon Dioxide	3.58	3.58	3.58	3.58	3.58	3.58	3.57	3.57	3.58	3.58
	Magnesium Stearate	7.15	7.15	7.15	7.15	7.15	7.15	7.13	7.13	7.15	7.15

*All weights in mg.

III. Methods for Preparing Solid Dosage Forms of the Pharmaceutical Composition

Another aspect of the disclosure provides methods for preparing solid dosage forms of the pharmaceutical composition that provide extended release of oxycodone and acetaminophen. Solid dosage compositions in the form of tablets may be produced using any suitable method known in the art including but not limited to wet granulation, dry granulation, direct compression, and combinations thereof.

Granulation is a manufacturing process which increases the size and homogeneity of active pharmaceutical ingredients and excipients that comprise a solid dose composition. The granulation process, which is often referred to as agglomeration, changes important physical characteristics of the dry composition, with the aim of improving manufacturability and, thereby, product quality, as well as providing desired release kinetics. Wet granulation is by far the more prevalent agglomeration process utilized within the pharmaceutical industry. Most wet granulation procedures follow some basic steps; the active agent(s) and excipients are mixed together, and a binder solution is prepared and added to the powder mixture to form a wet mass. The moist particles are then dried and sized by milling or by screening through a sieve. In some cases, the wet granulation is “wet milled” or sized through screens before the drying step. The wet granulation process may be a high shear granulation process or a fluid bed granulation process. Several methods of granulation are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety.

After granulation and drying of the resultant particles, batches are characterized with respect to properties such as final Loss on Drying (LOD), bulk density, tap density, and particle size. Loss on Drying (LOD) typically is determined after each granulation using the Moisture Analyzer. Several 1 g samples may be taken and loaded into the moisture analyzer. The samples may be run for 5 minutes at a temperature of 105° C. In another embodiment, the samples may be run at 105° C. until there is no weight fluctuation in order to determine the LOD.

Bulk and tap densities may be determined as follows. A graduated cylinder is filled with a certain amount of material (e.g., 30-40 g or 82-88 g), and the volume recorded to determine the material bulk density. Tap density can be determined with a help of a Tap Density Tester by exposing the material to 100 taps per test and recording the new volume.

Particle size determination generally is performed immediately after granulation, after sieving through 20 mesh screen to remove agglomerates. Particle diameter may be determined with a sieve-type particle diameter distribution gauge using sieves with openings of 30, 40, 60, 80, 120, and 325 mesh. Fractions may be weighed on a Mettler balance to estimate size distribution. This provides determination of the quantitative ratio by particle diameter of composition comprising extended release particles. Sieve analysis according to standard United States Pharmacopeia methods (e.g., USP-23 NF 18), may be done such as by using a Meinzer II Sieve Shaker.

In one embodiment, the method for preparing dosage forms of the pharmaceutical composition may comprise wet granulating a first mixture comprising oxycodone, acetaminophen, and a binder to produce a first granulation mixture. The wet granulation process may be a fluid bed granulation process. In additional embodiments, the first mixture may further comprise at least one additional excipient selected from the group consisting of fillers, lubricants, antioxidants, chelating agents, and color agents. The first granulation mixture may be blended with an extended release polymer and one or more excipients, as listed above, to form at least one extended release portion of a dosage form. In certain embodiments, the extended release polymer may be a polyethylene oxide.

In another embodiment, the method further comprises wet granulating a second mixture comprising oxycodone, acetaminophen, and a binder to form a second granulation mixture. The wet granulation process may be a fluid bed granulation process. In some embodiments, the second mixture may further comprise at least one additional excipient selected from the group consisting of fillers, lubricants, disintegrants, antioxidants, chelating agents, and color agents.

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The second granulation mixture may be blended with one or more excipients, as listed above, to form an immediate release portion of a dosage form.

In an additional embodiment, the method may further comprise compressing the at least one extended release portion and the at least one immediate release portion into a tablet. The tablet may be a bilayer tablet. The tablet may be coated with a tablet coating.

In another embodiment, the method may comprise granulating via a high shear wet granulation process a mixture comprising oxycodone and at least one excipient to form oxycodone particles. The oxycodone particles may be dried at a suitable temperature. The oxycodone particles comprising oxycodone may be granulated via a fluid bed granulation process with acetaminophen, a binder, and an optional excipient to form the granulation mixture. The granulation mixture may be blended with an extended release polymer and at least one excipient to form an extended release portion of a solid dosage form.

In a further embodiment, the method may further comprise granulating via a fluid bed granulation process oxycodone particles comprising oxycodone with acetaminophen, a binder, and an optional excipient to form another granulation mixture. This granulation mixture may be blended with one or more excipients to form an immediate release portion of a solid dosage form.

In an additional embodiment, the method may further comprise compressing the at least one extended release portion comprising oxycodone particles and the at least one immediate release portion comprising oxycodone particles into a tablet. In one embodiment, the method comprises compressing one extended release portion comprising the oxycodone particles and one immediate release portion comprising the oxycodone particles into a bilayer tablet. The tablet may be coated with a tablet coating.

In another embodiment, wet granulation of either mixture may produce particles with a bulk density ranging from about 0.30 to 0.40 grams/milliliter (g/mL). In other aspects, the wet granulation may produce particles with a tap density ranging from about 0.35 g/mL to about 0.45 g/mL. In other embodiments, the wet granulation may produce particles, wherein at least about 50% of the particles have a size greater than 125 microns. In still other embodiments, the wet granulation may produce particles wherein about 20% to about 65% of the particles have a size greater than about 125 microns and less than about 250 microns.

Tablets generally are characterized with respect to disintegration and dissolution release profiles as well as tablet hardness, friability, and content uniformity.

In vitro dissolution profiles for the tablets may be determined using a USP Type II apparatus, with a paddle speed of either about 100 rpm or 150 rpm, in 0.1 N HCl, at 37° C. Samples of 5 ml at each time-point may be taken without media replacement at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hours, for example. In some embodiments, the dissolution profiles may be determined at varying pH values, such as at a pH of about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 or 6.5. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. The resulting cumulative dissolution profiles for the tablets are based upon a theoretical percent active added to the compositions.

A tablet preferably disintegrates before it dissolves. A disintegration tester measures the time it takes a tablet to break apart in solution. The tester suspends tablets in a solution bath for visual monitoring of the disintegration rate. Both the time to disintegration and the disintegration consistency of all tablets may be measured. The disintegration profile may be

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determined in a USP Disintegration Tester in 0.1 N HCl of pH 1.2. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. Samples, 1-5 ml at each time-point, may be taken, for example, without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profiles are based upon a theoretical percent active added to the pharmaceutical compositions.

After tablets are formed by compression, it is desired that the tablets have a strength of at least 9-25 Kiloponds (kp), or at least about 12-20 kp. A hardness tester generally is used to determine the load required to diametrically break the tablets (crushing strength) into two equal halves. The fracture force may be measured using a Venkel Tablet Hardness Tester, using standard USP protocols.

Friability is a well-known measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability properties are especially important during any transport of the dosage form as any fracturing of the final dosage form may result in a subject receiving less than the prescribed medication. Friability may be determined using a Roche Friability Drum according to standard USP guidelines which specifies the number of samples, the total number of drum revolutions, and the drum rpm to be used. Friability values of from 0.8 to 1.0% generally are regarded as constituting the upper limit of acceptability.

The prepared tablets generally are tested for content uniformity to determine if they meet the pharmaceutical requirement of an acceptance value of 15 or less. Each tablet may be placed in a solution of 60% methanol/40% isopropanol and stirred at room temperature until the tablet disintegrates. The solution containing the dissolved tablet may be further diluted in 90% water/10% isopropanol/0.1% heptafluorobutyric acid and generally is analyzed by HPLC.

IV. Method for Reducing the Risk of Acetaminophen-Induced Hepatic Damage

The present disclosure also provides methods for reducing the risk of acetaminophen-induced hepatic damage in a subject being treated for pain with a dosage regimen that comprises administering to the subject at least two consecutive doses of a pharmaceutical composition comprising oxycodone and acetaminophen. The method comprises administering a first dose of a pharmaceutical composition comprising at least one extended release portion comprising the acetaminophen, the oxycodone or a combination thereof, and an extended release component to the subject, wherein the composition maintains a therapeutic blood plasma concentration of oxycodone of at least 5 ng/mL from about 0.75 hours to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration. The method further comprises administering a second dose of the pharmaceutical composition to the subject at about 12 hours after administration of the first dose.

Avoiding toxic intermediate formation is an important strategy in addressing product safety. Indeed, acetaminophen is absorbed from the stomach and small intestine and primarily metabolized by conjugation in the liver to nontoxic, water-soluble compounds that are eliminated in the urine. When the maximum daily dose ("MDD") is exceeded over a prolonged period, metabolism by conjugation becomes satu-

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rated, and excess acetaminophen is oxidatively metabolized by the CYP enzymes (CYP2E1, 1A2, 2A6, 3A4) to a reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). NAPQI has an extremely short half-life, and rapidly conjugates with available glutathione, which acts as a sulfhydryl donor. The reduced NAPQI is then renally excreted. The liver plays a central role in the turnover of glutathione in the body. Given that toxicity due to NAPQI formation occurs via necrosis of the liver following the formation of toxic adducts, minimizing glutathione depletion and enhancing glutathione regeneration in the liver is an important concern.

Human erythrocyte data resulting from hepatic turnover demonstrate a time-delayed response to redox and free radical insults via glutathione depletion and regeneration. The hepatic dynamics of glutathione formation and depletion in animal data using hepatic models can also be reviewed. In Swiss mice, the dynamics of glutathione depletion was investigated in detail for acetaminophen doses ranging from (100 mg/kg to 600 mg/kg) in work done by Brzezinska and Piotrowski (1989). Under one embodiment of the present invention, the intended dosage for patients with acute pain is 1.3 g/day of acetaminophen. Assuming a subject's weight of 70 kg, this is 1.229×10^{-4} moles/kg/day in human subjects. In Swiss mice, 400 mg/kg and 600 mg/kg are 2.65×10^{-3} moles/kg/day and 3.97×10^{-3} moles/kg/day, respectively, resulting in a 22-fold and a 32-fold safety exposure ratio, as compared with human levels. The bioequivalence level is 95%. Brzezinska and Piotrowski report that circulating hepatic GSH changes in mice began within 15 min after acetaminophen administration, and depletion followed a pattern that was strictly dose dependent, reaching a minimum GSH level 2 hrs after injection for the all dose groups, rebounding to initial levels between hours 8 and 12. Taken together, these results support the hypothesis that exposing subjects to the lower end of the therapeutic window of acetaminophen may provide benefit in terms of the patient's ability to regenerate physiologically protective levels of glutathione. Thus, the pharmaceutical formulations disclosed herein, which are designed to allow for a two hour break in acetaminophen exposure in each twelve hour exposure window allows for restorative hepatic regeneration of the subject's glutathione levels during that period when the acetaminophen concentrations are at their lowest or absent, while still preserving the considerable benefits of the potentiating effects of combination analgesia.

As mentioned above, acetaminophen is primarily metabolized via conjugation reactions, e.g., glucuronidation and sulfation, in the liver to nontoxic, water-soluble compounds that are rapidly eliminated from the body. A small proportion of acetaminophen is metabolized by the cytochrome P450 system to the reactive metabolite, NAPQI. Generally, this toxic metabolite is rapidly detoxified by conjugation to glutathione to form a non-toxic metabolite that is renally excreted. However, if the conjugation pathways become saturated and more acetaminophen is metabolized via the cytochrome P450 pathway, the pool of available glutathione may become depleted. With insufficient glutathione to bind to and inactivate NAPQI, this toxic metabolite is able to react with the sulfhydryl groups of cellular proteins initiating a cascade of cellular damage, which may lead to liver necrosis, and, ultimately, liver failure.

The method disclosed herein addresses the problem of depleted stores of glutathione by providing a period of time during the later part of the dosing interval during which the release of acetaminophen is low because most of the acetaminophen has already been released from the composition. The period of time during which the release of acetaminophen is

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low is called the acetaminophen "time-off" period. As a consequence of this acetaminophen time-off period, the plasma levels of acetaminophen fall to sufficiently low levels such that the metabolic burden on the liver is reduced, thereby allowing the depleted stores of glutathione to be replenished via the continuous glutathione manufacturing pathway comprising the glutathione synthase pathway. Because the levels of glutathione are able to be restored before the next dose, the risk of acetaminophen-induced hepatic damage is significantly reduced.

Additionally, the acetaminophen time-off period provided by the compositions disclosed herein may provide an added and beneficial precaution for any subject undergoing acetaminophen therapy to avoid an inadvertent reduction in glutathione stores and any potential acetaminophen-induced hepatic damage. In particular, the acetaminophen time-off period provided by the compositions disclosed herein may be especially useful during chronic administration of analgesic compositions comprising acetaminophen. The subject may be at increased risk for developing acetaminophen-induced hepatic damage because of frequent and regular user of alcohol (i.e., ethanol), concurrent administration of acetaminophen from another source (e.g., an over-the-counter medication), poor diet, and/or compromised liver function.

In general, the compositions disclosed herein are formulated such that the rate of release of acetaminophen is high during the first several hours of the dosing interval and the rate of release of acetaminophen is low during the last several hours of the dosing interval. More specifically, the compositions are formulated to release from about 40% to about 65% of the acetaminophen in about 30 minutes, from about 55% to about 80% of the acetaminophen in about 2 hours, from about 65% to about 92% of the acetaminophen in about 4 hours, and from about 67% to about 95% of the acetaminophen in about 8 hours, wherein the dosing interval is about 12 hours. In another, the compositions are formulated to release from about 45% to about 60% of the acetaminophen in about 30 minutes, from about 57% to about 75% of the acetaminophen in about 2 hours, from about 67% to about 90% of the acetaminophen in about 4 hours, and from about 70% to about 95% of the acetaminophen in about 8 hours, wherein the dosing interval is about 12 hours. In yet another embodiment, during the final 4 hours of a 12 hour dosing interval, only about 5% of the acetaminophen remains to be released from the composition.

The subject may be a mammal, and in certain embodiments, the subject may be a human. In various embodiments, the at least two consecutive doses of the analgesic composition may be administered to the subject at 8 hour intervals, 10 hour intervals, 12 hour intervals, 18 hour intervals, or 24 hour intervals.

The method for reducing the risk of acetaminophen-induced hepatic damage disclosed herein may further comprise administering additional doses of the pharmaceutical composition at regular dosing intervals, such as e.g., at 12 hour intervals. During the latter part of each dosing interval, therefore, the acetaminophen time-off period allows depleted stores of glutathione to be replenished, thereby reducing the risk of acetaminophen-induced hepatic damage in subjects being treated for pain with a composition comprising acetaminophen.

V. Method for Treating Pain

Also provided is a method for treating pain in a subject in need of such treatment with a pharmaceutical composition that comprises oxycodone and acetaminophen, wherein the

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method comprises administering an effective amount of any of the pharmaceutical compositions disclosed herein. The method comprises orally administering to the subject an effective amount of a pharmaceutical composition comprising at least one extended release portion comprising oxycodone, acetaminophen and combination thereof, and an extended release component, wherein the composition maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration.

In some embodiments, the subject may be suffering from or diagnosed with chronic pain. In yet another embodiment, the subject may be suffering from or diagnosed with acute pain. In still another embodiment, the subject may be suffering from or diagnosed with moderate to severe acute pain. In yet other embodiments, the subject may be suffering from or diagnosed with both chronic and acute pain. The subject may be a mammal, and in certain embodiments, the subject may be a human.

In one embodiment, the effective amount of a pharmaceutical composition may be 15 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 15 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 7.5 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 7.5 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 7.5 mg of oxycodone and 325 mg of acetaminophen may be administered. In yet another embodiment, the effective amount of a pharmaceutical composition may be 20 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 20 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 10 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 10 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 10 mg of oxycodone and 325 mg of acetaminophen may be administered. In still yet another embodiment, the effective amount of a pharmaceutical composition may be 30 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 30 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 15 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 15 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 15 mg of oxycodone and 325 mg of acetaminophen may be administered.

The dosing intervals of the effective amount of the pharmaceutical composition can and will vary. For example, an effective amount of the pharmaceutical composition may be administered once a day, twice a day, or three times a day. In another embodiment, an effective amount of the pharmaceutical composition may be administered twice a day.

In general, therapeutic plasma concentrations of oxycodone and acetaminophen are attained within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30

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minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the first dose of the pharmaceutical composition. Accordingly, depending upon the severity of the pain, onset of analgesia may be attained within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition. Onset of analgesia may be measured by the double stopwatch method or other pain assessments as described in Example 12 below. Generally, analgesia or pain relief will be maintained throughout the duration of the dosing interval. For example, in one embodiment, analgesia or pain relief will be maintained for 12 hours. Upon administration of the next dose of the pharmaceutical composition, therefore, analgesia or pain relief may be maintained. Accordingly, analgesia or pain relief will be maintained as long as therapeutic amounts of the pharmaceutical composition are administered at regular dosing intervals. Moreover, pain relief may be managed such that no breakthrough episodes of pain occur.

In some embodiments, an effective amount of the pharmaceutical composition may be administered to a subject in a fed state. In general, a fed state is defined as having consumed food within about 30 min prior to administration of the pharmaceutical composition. The food may be a high fat meal, a low fat meal, a high calorie meal, or a low calorie meal. In other embodiments, an effective amount of the pharmaceutical composition may be administered to a subject in a fasted state. In general, a fasted state is defined as not having ingested food for at least 10 hours prior to administration of the pharmaceutical composition. In some embodiments, the pharmaceutical composition may be administered to a subject who has fasted for at least 10 hours prior to the first dose and who fasts for at least one hour prior to administration of subsequent doses. In other embodiments, the pharmaceutical composition may be administered to a subject who has fasted for at least 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours prior to administration of each dose.

The method of the present invention is useful for treating numerous pain states that are currently being treated with conventional immediate release compositions comprising acetaminophen and oxycodone. These and additional pain states include, by way of illustration and not limitation, headache pain, pain associated with migraine, neuropathic pain selected from the group consisting of diabetic neuropathy, HIV sensory neuropathy, post-herpetic neuralgia, post-thoracotomy pain, trigeminal neuralgia, radiculopathy, neuropathic pain associated with chemotherapy, reflex sympathetic dystrophy, back pain, peripheral neuropathy, entrapment neuropathy, phantom limb pain, and complex regional pain syndrome, dental pain, pain associated with a surgical procedure and or other medical intervention, bone cancer pain, joint pain associated with psoriatic arthritis, osteoarthritic pain, rheumatoid arthritic pain, juvenile chronic arthritis associated pain, juvenile idiopathic arthritis associated pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome) associated pain), pain associated with psoriatic arthritis, gout pain, pain associated with pseudogout (pyrophosphate arthritis), pain associated with systemic lupus erythematosus (SLE), pain associated with systemic sclerosis (scleroderma), pain associated with Behcet's disease, pain associated with relapsing polychondritis, pain associated with adult Still's disease, pain associated with transient regional osteoporosis, pain associated with neuropathic arthropathy, pain associated with sarcoidosis, arthritic pain, rheumatic pain, joint pain, osteoar-

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thritic joint pain, rheumatoid arthritic joint pain, juvenile chronic arthritis associated joint pain, juvenile idiopathic arthritis associated joint pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome) associated joint pain), gout joint pain, joint pain associated with pseudogout (pyrophosphate arthritis), joint pain associated with systemic lupus erythematosus (SLE), joint pain associated with systemic sclerosis (scleroderma), joint pain associated with Behcet's disease, joint pain associated with relapsing polychondritis, joint pain associated with adult Still's disease, joint pain associated with transient regional osteoporosis, joint pain associated with neuropathic arthropathy, joint pain associated with sarcoidosis, arthritic joint pain, rheumatic joint pain, acute pain, acute joint pain, chronic pain, chronic joint pain, inflammatory joint pain, inflammatory joint pain, mechanical pain, mechanical joint pain, pain associated with the fibromyalgia syndrome (FMS), pain associated with polymyalgia rheumatica, monarticular joint pain, polyarticular joint pain, nociceptive pain, psychogenous pain, pain of unknown etiology, pain mediated by IL-6, IL-6 soluble receptor, or IL-6 receptor, pain associated with a surgical procedure in a patient with a clinical diagnosis of OA, pain like static allodynia, pain like dynamic allodynia, and/or pain associated with Crohn's disease.

Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

EXAMPLES

The following examples are included to demonstrate certain embodiments of the invention. Those of skill in the art should, however, in light of the present disclosure, appreciate that modifications can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth is to be interpreted as illustrative and not in a limiting sense.

Example 1

In Vitro Dissolution of Controlled-Release Bilayer Tablets

Control-release bilayer tablets were prepared containing 15 mg of oxycodone and 500 mg of acetaminophen (APAP), or 30 mg of oxycodone and 500 mg APAP. (See selected examples from Chart No. 2.) The ER layer contained 75% of the total amount of oxycodone in the tablet, 50% of the total amount of APAP in the tablet, and either 35% w/w POLYOX® 1105 (for fast release), 45% w/w POLYOX® 1105 (for medium release), or 45% w/w POLYOX® N60K (for slow release). The IR layer contained 25% of the total amount of oxycodone in the tablet and 50% of the total amount of APAP in the tablet.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel that contained 900 mL of (helium sparged) 0.1 N HCl that was heated to 37° C. ± 0.5° C. The mixture was stirred at 150 ± 6 rpm and the temperature was maintained at 37° C. ± 0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

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The cumulative release of oxycodone and APAP from 15 mg oxycodone/500 mg APAP tablets is presented in Table 1. Table 2 presents the cumulative release of oxycodone and APAP from 30 mg oxycodone/500 mg APAP (30/500) tablets. FIG. 1 presents the release profile of oxycodone from the 15/500 and 30/500 tablets. The dissolution profile of APAP from the 15/500 and 30/500 tablets is shown in FIG. 2. The release of oxycodone and APAP from the fast release and medium release tablets was essentially linear during the first half of the 12 hour time period but then plateaued during the last half of the 12 hour time period. The release of oxycodone and APAP from the slow release tablets was essentially linear during the entire 12 hour time period.

TABLE 1

Cumulative Release- 15 mg oxycodone/500 mg APAP Tablets						
Time (hr)	Oxycodone (%)			APAP (%)		
	Fast	Medium	Slow	Fast	Medium	Slow
0.25	27.56	25.70	25.68	54.78	53.06	53.01
0.5	34.33	31.31	30.39	57.55	55.73	54.89
1.0	—	40.85	37.81	—	60.03	58.03
2.0	59.88	55.67	49.50	71.42	68.16	63.27
4.0	83.46	77.94	67.43	86.17	81.55	72.31
6.0	97.48	92.12	80.53	96.19	91.62	79.97
8.0	101.26	99.26	90.20	100.16	96.96	86.06
12.0	101.57	101.23	99.36	100.10	99.16	94.41

TABLE 2

Cumulative Release- 30 mg oxycodone/500 mg APAP Tablets						
Time (hr)	Oxycodone (%)			APAP (%)		
	Fast	Medium	Slow	Fast	Medium	Slow
0.25	31.65	30.27	29.78	54.17	52.97	52.97
0.5	37.55	35.91	34.42	56.96	55.64	54.97
1.0	47.18	45.21	41.12	61.81	60.19	58.15
2.0	62.51	59.63	52.40	70.60	68.04	63.61
4.0	84.72	80.44	70.01	85.28	81.56	73.04
6.0	96.97	93.98	82.49	94.57	91.42	80.94
8.0	100.23	99.63	91.78	97.91	96.48	87.26
12.0	100.57	101.13	99.60	98.09	98.14	95.25

The cumulative in vitro release of oxycodone and APAP from 7.5 mg oxycodone/325 mg APAP medium release tablets is presented in Table 3. The ER layer of these tablets contained 5.625 mg of oxycodone, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105, and the IR layer contained 1.875 mg of oxycodone and 162.5 mg of APAP. (See selected example from Chart 1.) The dissolution profile was determined essentially as described above, except that samples were collected at 0.08 hour (~5 min) in addition to the later time points.

TABLE 3

Cumulative Release 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Oxycodone (%)		APAP (%)	
	Mean (%)	% RSD (6)	Mean (%)	% RSD (%)
0.08	26.6	4.3	49.0	3.4
0.25	31.5	4.2	51.3	3.1

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TABLE 3-continued

Cumulative Release 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Oxycodone (%)		APAP (%)	
	Mean (%)	% RSD (6)	Mean (%)	% RSD (%)
0.5	37.5	2.7	53.8	2.9
1.0	45.9	1.6	58.2	2.5
2.0	60.1	1.7	66.0	2.3
4.0	81.4	1.1	78.7	1.7
6.0	95.4	1.4	88.4	1.9
8.0	101.8	0.9	93.9	1.4
12.0	103.2	1.2	94.9	1.1

FIG. 3 and FIG. 4 present the percentage of oxycodone and APAP, respectively, released from two different lots of 7.5/325 tablets as compared to 15/650 tablets (see Example 28 for the dissolution data of the 15 mg oxycodone/650 acetaminophen tablets). The dissolution profiles were similar among all the tablets.

The release of oxycodone and APAP from each layer was analyzed by determining the calculated release from the ER layer and actual release from the total composition. For this, the tablets contained 7.5 mg of oxycodone HCl and 325 mg of APAP (i.e., the ER layer contained 5.625 mg of oxycodone HCl, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105; and the IR layer contained 1.875 mg of oxycodone HCl and 162.5 mg of APAP). The dissolution profile was determined essentially as described above. The calculated cumulative release of oxycodone HCl from the ER layer and the total tablet is presented in Table 4, and the calculated cumulative release of APAP from the ER layer and the total tablet is presented in Table 5. These data show that essentially all of the 1.875 mg of oxycodone HCl in the IR layer was released within about 5 minutes and essentially all of the 162.5 mg of APAP in the IR layer was released within about 15 minutes.

TABLE 4

Split Release of Oxycodone 7.5 mg oxycodone/ 325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
0.08	26.6	2.00	2.1	0.12
0.25	31.5	2.36	8.7	0.49
0.5	37.5	2.81	16.7	0.94
1.0	45.9	3.44	27.9	1.57
2.0	60.1	4.51	46.8	2.63
4.0	81.4	6.11	75.2	4.23
6.0	95.4	7.16	93.9	5.28
8.0	101.8	7.64	102.4	5.76
12.0	103.2	7.74	104.3	5.87

TABLE 5

Split Release of APAP 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
0.08	49.0	159.25	0.0	0.00
0.25	51.3	166.73	2.6	4.22
0.5	53.8	174.85	7.6	12.35
1.0	58.2	189.15	16.4	26.65
2.0	66.0	214.50	32.0	52.00
4.0	78.7	255.78	57.4	93.28
6.0	88.4	287.30	76.8	124.80

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TABLE 5-continued

Split Release of APAP 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
8.0	93.9	305.18	87.8	142.68
12.0	94.9	308.43	89.8	145.93

Example 2

Clinical Pharmacokinetic Analysis of Controlled-Release 15 mg Oxycodone/500 mg Acetaminophen Bilayer Tablets—Single Dose

An open-label, single dose, four-period crossover study was conducted to evaluate the pharmacokinetics (PK) and bioavailability of three controlled-release bilayer tablets comprising 15 mg oxycodone (OC) and 500 mg APAP as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen. The three controlled release formulations—fast, medium, and slow—are described above. (See selected examples from Chart No. 2.) One tablet of each of the controlled-release bilayer formulations was administered to the test subjects under fed conditions. One tablet of the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen was administered every 6 hours (Q6h) for two doses under fed conditions. The test subjects were about 40 normal, healthy male subjects between 21-45 years of age.

Subjects were randomly assigned to Treatments A, B, C, and D using a four-period, eight-sequence, crossover design as follows:

Treatment A: One (1) tablet of 15 mg OC/500 mg APAP, Fast Release administered orally under fed conditions.

Treatment B: One (1) tablet of 15 mg OC/500 mg APAP, Medium Release administered orally under fed conditions.

Treatment C: One (1) tablet of 15 mg OC/500 mg APAP, Slow Release administered orally under fed conditions.

Treatment D: One (1) tablet of a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg administered orally Q6h for two (2) doses under fed conditions.

The crossover design allowed for within-subject comparisons among the test formulations with differing release profiles. Subjects received each of the study drug treatments (A-D) separated by at least a 7-day interval between the start of each period at Hour 0. During each period, subjects remained in the clinical facility from the time of check-in (on the day prior to dosing) until discharge on Day 3 (after the 48 hour blood draw).

Physical examinations, electrocardiograms and clinical laboratory tests were performed at screening and at the conclusion of the study (or early termination). Vital sign measurements (including pulse oximetry) and adverse events were monitored during the study. Subjects were administered a 50 mg naltrexone tablet 12 hours prior to Hour 0 dosing, at Hour 0, and 12 hours post-dose to block the effects and potential risks of oxycodone. After a 10 hour overnight fast, subjects were served a standardized FDA high-fat breakfast to be consumed in 30 minutes or less prior to Hour 0 dosing for the first oral dosage. All subjects in each period were served a standardized meal to be consumed in 30 minutes or less

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prior to Hour 6. Only subjects randomized to Treatment D were administered the second oral dosage of the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen at Hour 6 in each period.

Blood was drawn at designated times for PK analysis. Samples (6 mL in pre-chilled vacuum blood collection tubes, containing K2EDTA as the anticoagulant) were taken pre-dose (up to 60 minutes prior to dose), 10 min, 20 min, 30 min, 40 min and 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36 and 48 hours post-dose. The collected plasma samples were analyzed for the active pharmaceutical ingredients (APIs), i.e., oxycodone and acetaminophen, using validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays.

The following PK parameters were calculated for oxycodone and acetaminophen using standard non-compartmental methods:

area under the plasma concentration curve to last quantifiable concentration $AUC_{(0-t)}$
 area under the plasma concentration curve to infinite time $AUC_{(0-inf)}$
 maximum observed plasma concentration (C_{max})
 time observed maximum plasma concentration (t_{max})
 lag time (t_{lag})
 apparent first-order terminal elimination rate constant (k_{el})
 apparent plasma terminal elimination half-life ($t_{1/2}$)

Parametric general linear model (GLM) methodology was used in the analysis of all pharmacokinetic parameters. The SAS GLM procedure was used to perform analysis of variance (ANOVA) on each pharmacokinetic parameter with sequence, treatment, period, and subjects nested within sequences, as sources of variation. For each formulation, least squares means and the associated standard errors were obtained using the LSMEANS option. All treatment pairwise comparisons were performed, without adjustment for multiplicity. AUC and C_{max} were dose-adjusted for comparative purposes for acetaminophen and the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen.

The pharmacokinetic data for oxycodone and APAP are presented in Tables 6-8 and 9-11, respectively.

TABLE 6

Oxycodone Pharmacokinetics (15/500)						
Parameter	Fast Release Formulation				Commercially available immediate-release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{max} (ng/mL)	18.803 (21)	82.92	78.02	88.12	22.428 (20)	
C_{1hr} (ng/mL)	6.891 (77)	72.79	49.02	108.1	10.226 (65)	
C_{2hr}^a (ng/mL)	12.355 (32)	80.74	71.2	91.56	14.94 (26)	
AUC_{0-t} (ng · hr/mL)	209.949 (26)	89.73	86.52	93.06	229.788 (22)	
AUC_{0-inf} (ng · hr/mL)	211.8 (25)	89.95	86.77	93.24	231.421 (22)	
AUC_{0-1hr} (ng · hr/mL)	2.565 (104)	61.32	37.64	99.92	4.334 (80)	
AUC_{0-2hr}^b (ng · hr/mL)	12.189 (53)	70.16	55.97	87.95	16.917 (46)	

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TABLE 6-continued

Oxycodone Pharmacokinetics (15/500)					
Parameter	Fast Release Formulation				Commercially available immediate-release tablet
	Mean	LSM	90% CI		
	(% CV)	Ratio	Lower	Upper	
AUC_{0-4hr}^c (ng · hr/mL)	41.3 (29)	88.76	80.61	97.73	45.699 (24)
T_{max} (hr)	4.954 (34)	na	na	na	7.954 (22)
T_{lag} (hr)	0.31 (68)	na	na	na	0.219 (77)
$T_{1/2}$ (hr)	4.584 (17)	na	na	na	4.495 (14)
K_{el} (1/hr)	0.155 (16)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet

^bAUC from zero the median T_{max} for commercially-available immediate release tablet

^cAUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

TABLE 7

Oxycodone Pharmacokinetics (15/500)					
Parameter	Medium Release Formulation				Commer- cially- available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	18.266 (25)	80.87	76.09	85.95	22.428 (20)
C_{1hr} (ng/mL)	7.364 (81)	67.62	45.75	99.95	10.226 (65)
C_{2hr}^a (ng/mL)	12.388 (45)	79.04	69.69	89.64	14.94 (26)
AUC_{0-t} (ng · hr/mL)	217.188 (23)	94.19	90.82	97.68	229.788 (22)
AUC_{0-inf} (ng · hr/mL)	218.545 (23)	94.09	90.77	97.54	231.421 (22)
AUC_{0-1hr} (ng · hr/mL)	3.248 (118)	64.69	39.93	104.8	4.334 (80)
AUC_{0-2hr}^b (ng · hr/mL)	13.124 (70)	71.74	57.22	89.96	16.917 (46)
AUC_{0-4hr}^c (ng · hr/mL)	42.101 (43)	88.61	80.47	97.58	45.699 (24)
T_{max} (hr)	5.31 (38)	na	na	na	7.954 (22)
T_{lag} (hr)	0.264 (64)	na	na	na	0.219 (77)
$T_{1/2}$ (hr)	4.557 (16)	na	na	na	4.495 (14)
K_{el} (1/hr)	0.156 (16)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet

^bAUC from zero the median T_{max} for commercially-available immediate release tablet

^cAUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

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TABLE 8

Oxycodone Pharmacokinetics (15/500)						
Parameter	Slow Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{max} (ng/mL)	17.403 (25)	76.75	72.21	81.58	22.428 (20)	
C_{1hr} (ng/mL)	7.601 (79)	69.63	47.08	102.97	10.226 (65)	
C_{2hr}^a (ng/mL)	11.237 (39)	73.55	64.84	83.43	14.94 (26)	
AUC_{0-t} (ng · hr/mL)	222.096 (25)	95.62	92.2	99.18	229.788 (22)	
AUC_{0-inf} (ng · hr/mL)	223.553 (25)	95.61	92.22	99.11	231.421 (22)	
AUC_{0-1hr} (ng · hr/mL)	2.893 (112)	57.34	35.37	92.95	4.334 (80)	
AUC_{0-2hr}^b (ng · hr/mL)	12.312 (66)	68.63	54.72	86.08	16.917 (46)	
AUC_{0-4hr}^c (ng · hr/mL)	38.842 (35)	83.46	75.78	91.92	45.699 (24)	
T_{max} (hr)	5.655 (27)	na	na	na	7.954 (22)	
T_{lag} (hr)	0.299 (74)	na	na	na	0.219 (77)	
$T_{1/2}$ (hr)	4.647 (19)	na	na	na	4.495 (14)	
K_{el} (1/hr)	0.154 (18)	na	na	na	0.157 (13)	

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 9

Acetaminophen Pharmacokinetics (15/500)						
Parameter	Fast Release Formulation				Commercially-available immediate release tablet*	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C _{max} (ng/mL)	2612 (26)	94.46	87.25	102.26	2721 (22)	
C _{1hr} (ng/mL)	1627 (66)	113.22	84.91	150.98	1516 (58)	
C _{2hr} ^a (ng/mL)	2248 (30)	118.49	107.61	130.48	1841 (20)	
AUC _{0-t} (ng · hr/mL)	21944 (27)	98.78	95.91	101.75	21962 (22)	
AUC _{0-inf} (ng · hr/mL)	23090 (27)	98.73	95.85	101.7	23104 (21)	
AUC _{0-1hr} (ng · hr/mL)	823 (96)	105.42	68.75	161.64	814 (82)	
AUC _{0-2hr} ^b (ng · hr/mL)	2761 (52)	106.73	86.55	131.62	2492 (47)	
AUC _{0-4hr} ^c (ng · hr/mL)	7006 (28)	119.91	110.42	130.2	5726 (22)	
T _{max} (hr)	2.328 (58)	na	na	na	6.971 (34)	
T _{lag} (hr)	0.276 (81)	na	na	na	0.219 (98)	

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TABLE 9-continued

Acetaminophen Pharmacokinetics (15/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet*
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
T _{1/2} (hr)	5.235 (35)	na	na	na	6.461 (66)
K _{el} (1/hr)	0.145 (28)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 10

Acetaminophen Pharmacokinetics (15/500)					
	Medium Release Formulation				Commercially-available immediate release tablet*
	Mean	LSM	90% CI		Mean
Parameter	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2720 (22)	99.19	91.61	107.39	2721 (22)
C_{1hr} (ng/mL)	1831 (54)	121.62	91.51	161.65	1516 (58)
C_{2hr}^a (ng/mL)	2170 (23)	116.69	105.96	128.51	1841 (20)
AUC_{0-t} (ng · hr/mL)	22184 (22)	100.68	97.74	103.7	21962 (22)
AUC_{0-inf} (ng · hr/mL)	23554 (22)	101.39	98.43	104.44	23104 (21)
AUC_{0-1hr} (ng · hr/mL)	974 (85)	124.39	81.52	189.79	814 (82)
AUC_{0-2hr}^b (ng · hr/mL)	2974 (47)	117.9	95.58	145.43	2492 (47)
AUC_{0-4hr}^c (ng · hr/mL)	7122 (23)	123.98	114.17	134.64	5726 (22)
T_{max} (hr)	2.069 (66)	na	na	na	6.971 (34)
T_{lag} (hr)	0.218 (77)	na	na	na	0.219 (98)
$T_{1/2}$ (hr)	5.696 (33)	na	na	na	6.461 (66)
K_{el} (1/hr)	0.133 (29)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

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TABLE 11

Acetaminophen Pharmacokinetics (15/500)					
	Slow Release Formulation				Commer- cially- available immediate release tablet*
	Mean	LSM	90% CI		Mean
Parameter	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2521 (18)	93.6	86.44	101.35	2721 (22)
C_{1hr} (ng/mL)	1766 (51)	126.26	94.96	167.87	1516 (58)
C_{2hr}^a (ng/mL)	2113 (18)	116.18	105.48	127.96	1841 (20)
AUC_{0-t} (ng · hr/mL)	21947 (25)	99.61	96.7	102.61	21962 (22)
AUC_{0-inf} (ng · hr/mL)	23279 (25)	100.47	97.53	103.49	23104 (21)
AUC_{0-1hr} (ng · hr/mL)	872 (83)	115.25	75.49	175.95	814 (82)
AUC_{0-2hr}^b (ng · hr/mL)	2811 (43)	116.49	94.42	143.73	2492 (47)
AUC_{0-4hr}^c (ng · hr/mL)	6828 (19)	120.68	111.11	131.07	5726 (22)
T_{max} (hr)	2.184 (59)	na	na	na	6.971 (34)
T_{lag} (hr)	0.253 (86)	na	na	na	0.219 (98)
$T_{1/2}$ (hr)	5.366 (32)	na	na	na	6.461 (66)
K_{el} (1/hr)	0.141 (28)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

The pharmacokinetic parameters for the medium release 15/500 formulation and the commercially-available immediate release tablet are shown in Table 12.

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TABLE 12

Pharmacokinetic Profile (Mean ± SD) of Oxycodone/APAP versus commercially-available immediate release tablet (N = 29)						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/ mL)	AUC_{0-inf} (ng · hr/ mL)	T_{max} (hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Oxycodone						
15 mg OC/ 500 mg APAP	18.3 ± 4.6	217 ± 49.2	219 ± 49.5	5.3 ± 2.0	0.156 ± 0.024	4.6 ± 0.7
Com- mercially- available immediate release tablet (7.5 mg OC/325 mg APAP)	22.4 ± 4.5*	230 ± 49.8	231 ± 50.0	8.0 ± 1.7*	0.157 ± 0.020	4.5 ± 0.6
Acetaminophen						
15 mg OC/ 500 mg APAP	2720 ± 608	221184 ± 4804	23554 ± 5234	2.1 ± 1.4	0.133 ± 0.039	5.7 ± 1.9
Com- mercially- available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	2721 ± 584*	21962 ± 4772	23104 ± 4882	7.0 ± 2.4*	0.137 ± 0.054	6.5 ± 4.3

*Most values occurred after the second dose.

^aAUC and C_{max} dose-normalized to 500 mg for APAP.

35 The oxycodone mean plasma concentration as a function of time after administration of 15/500 tablets is shown in Table 13 and FIG. 5. The APAP mean plasma concentration over time after administration of 15/500 tablets is shown in Table 14 and FIG. 6.

TABLE 13

Time Course of Oxycodone Plasma Concentration (ng/mL)								
Time (hr)	Mean Fast	SEM	Mean Medium	SEM	Mean Slow	SEM	Mean commercially- available immediate release tablet	SEM
0	0	0	0	0	0	0	0	0
0.17	0	0	0.13	0.11	0.06	0.02	0.03	0.03
0.33	0.65	0.29	1.08	0.44	0.93	0.41	1.16	0.36
0.5	2.09	0.55	2.98	0.95	2.55	0.96	4.03	0.9
0.67	3.74	0.91	5.29	1.25	4.15	1.1	7.04	0.93
1	6.89	0.98	7.36	1.11	7.6	1.24	10.23	1.11
2	12.36	0.74	12.39	1.04	11.24	0.73	14.94	0.81
3	14.77	0.82	14.73	0.91	13.35	0.53	14.84	0.62
4	16.33	0.8	16.1	0.82	15.12	0.44	12.95	0.58
5	16.28	0.67	15.89	0.81	15.83	0.41	10.58	0.8
6	17.4	0.72	16.43	0.81	15.76	0.41	9.1	0.67
6.5	16.59	0.64	15.89	0.72	15.22	0.96	10.76	0.7
7	15.28	0.58	14.83	0.69	14.49	1.43	16.84	0.69
8	14.02	0.6	14.29	0.64	13.77	0.85	19.7	0.7
9	13.13	0.57	13.39	0.55	13	0.78	19.08	0.65
10	11.9	0.64	12.52	0.53	11.92	0.68	16.63	0.57
12	8.86	0.6	9.59	0.49	10.04	0.59	10.88	0.53

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TABLE 14

Time Course of Acetaminophen Plasma Concentration (ng/mL)								
Time (hr)	Mean Fast	SEM	Mean Medium	SEM	Mean Slow	SEM	Mean commercially-available immediate release tablet	SEM
0	0	0	0	0	0	0	0	0
0.17	31	18	284	151	220	88	107	47
0.33	673	210	751	221	678	197	607	173
0.5	1216	266	1299	275	1133	248	1181	229
0.67	1624	301	1922	301	1647	252	1653	255
1	2116	258	2380	239	2296	217	1971	210
2	2922	160	2821	123	2747	93	2393	90
3	2736	129	2719	90	2636	94	2150	65
4	2643	120	2524	103	2424	110	1717	71
5	2376	112	2246	121	2130	118	1290	59
6	2263	100	2080	143	1965	107	1006	58
6.5	2068	93	1903	126	1774	102	1742	212
7	1830	80	1744	116	1644	98	2749	232
8	1577	81	1573	103	1495	93	2790	114
9	1416	79	1407	88	1330	80	2482	111
10	1286	82	1314	84	1198	71	1968	105
12	1069	89	1131	86	1089	66	1188	82

Example 3

Clinical Pharmacokinetic Analysis of
Controlled-Release 30 mg Oxycodone/500 mg
Acetaminophen Bilayer Tablets—Single Dose

A single dose, four-period crossover study was conducted essentially as described in Example 2, except the controlled-release bilayer tablets contained 30 mg oxycodone and 500 mg APAP. (See selected examples from Chart No. 2.) Tables 15-17 and 18-20 present the PK data for oxycodone and APAP, respectively. The plasma concentrations of oxycodone and APAP are presented in FIG. 7 and FIG. 8, respectively.

TABLE 15

Oxycodone Pharmacokinetics (30/500)					
Parameter	Fast Release Formulation				
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	
C_{max} (ng/mL)	39.159 (28)	82.17	75.96	88.9	47.597 (26)
C_{1hr} (ng/mL)	20.462 (74)	77.25	54.37	109.76	25.911 (67)
C_{2hr}^a (ng/mL)	28.221 (39)	95.18	83.82	108.08	29.579 (32)
AUC_{0-t} (ng · hr/mL)	393.952 (30)	92.84	89.3	96.53	425.978 (29)
AUC_{0-inf} (ng · hr/mL)	396.135 (29)	92.4	88.94	95.99	430.196 (29)
AUC_{0-1hr} (ng · hr/mL)	9.106 (100)	71.09	46.05	109.76	11.55 (93)
AUC_{0-2hr}^b (ng · hr/mL)	33.448 (61)	82.59	67.9	100.46	39.295 (53)
AUC_{0-4hr}^c (ng · hr/mL)	96.47 (38)	101.27	91.51	112.06	93.706 (29)

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TABLE 15-continued

Oxycodone Pharmacokinetics (30/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
AUC_{4hr-t}^d (ng · hr/mL)	395.522 (29)	92.4	88.95	95.99	429.507 (29)
T_{max} (hr)	4.057 (51)	na	na	na	6.948 (33)
T_{lag} (hr)	0.213 (107)	na	na	na	0.184 (66)
$T_{1/2}$ (hr)	4.398 (15)	na	na	na	4.32 (15)
K_{el} (1/hr)	0.161 (15)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^b AUC from zero to the median T_{max} for commercially-available immediate release tablet^c AUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

TABLE 16

Oxycodone Pharmacokinetics (30/500)					
Parameter	Medium Release Formulation				Commercially- available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	36.731 (30)	77.14	71.27	83.48	47.597 (26)
C_{1hr} (ng/mL)	19.758 (70)	86.12	60.48	122.62	25.911 (67)
C_{2hr}^a (ng/mL)	27.655 (39)	93.53	82.31	106.28	29.579 (32)
AUC_{0-t} (ng · hr/mL)	396.026 (29)	94.17	90.55	97.92	425.978 (29)
AUC_{0-inf} (ng · hr/mL)	398.084 (29)	93.68	90.16	97.34	430.196 (29)
AUC_{0-1hr} (ng · hr/mL)	8.988 (85)	93.06	60.12	144.04	11.55 (93)
AUC_{0-2hr}^b (ng · hr/mL)	32.695 (56)	86.02	70.64	104.74	39.295 (53)
AUC_{0-4hr}^c (ng · hr/mL)	91.998 (36)	98.13	88.63	108.65	93.706 (29)
AUC_{4hr-t}^d	397.436 (29)	93.68	90.16	97.34	429.507 (29)
T_{max} (hr)	4.523 (51)	na	na	na	6.948 (33)
T_{lag} (hr)	0.207 (95)	na	na	na	0.184 (66)
$T_{1/2}$ (hr)	4.369 (14)	na	na	na	4.32 (15)
K_{el} (1/hr)	0.162 (14)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^b AUC from zero to the median T_{max} for commercially-available immediate release tablet^c AUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

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TABLE 17

Oxycodone Pharmacokinetics (30/500)					
Parameter	Slow Release Formulation				Commercially- available immediate release tablet
	Mean	LSM	90% CI		
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	32.976 (29)	68.96	63.74	74.6	47.597 (26)
C_{1hr} (ng/mL)	17.897 (74)	73.61	52.01	104.18	25.911 (67)
C_{2hr}^a (ng/mL)	23.183 (33)	78.42	69.06	89.05	29.579 (32)
AUC_{0-t} (ng · hr/mL)	399.623 (26)	94.5	90.9	98.25	425.978 (29)
AUC_{0-inf} (ng · hr/mL)	401.362 (26)	93.88	90.36	97.52	430.196 (29)
AUC_{0-1hr} (ng · hr/mL)	7.643 (96)	69.93	45.52	107.44	11.55 (93)
AUC_{0-2hr}^b (ng · hr/mL)	28.183 (59)	71.58	58.85	87.06	39.295 (53)
AUC_{0-4hr}^c (ng · hr/mL)	82.171 (36)	86.17	77.87	95.35	93.706 (29)
AUC_{4hr-t}^d	400.56 (26)	93.85	90.34	97.49	429.507 (29)
T_{max} (hr)	3.96 (48)	na	na	na	6.948 (33)
T_{lag} (hr)	0.201 (78)	na	na	na	0.184 (66)
$T_{1/2}$ (hr)	4.418 (17)	na	na	na	4.32 (15)
K_{el} (1/hr)	0.161 (17)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 18

Acetaminophen Pharmacokinetics (30/500)						
Parameter	Fast Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{max} (ng/mL)	3138 (32)	101.52	91.58	122.53	3085 (29)	
C_{1hr} (ng/mL)	2163 (59)	130.98	101.04	169.78	1777 (59)	
C_{2hr}^a (ng/mL)	2386 (32)	125.37	113.22	138.82	1892 (28)	
AUC_{0-t} (ng · hr/mL)	21742 (26)	98.53	95.07	102.13	21897 (23)	
AUC_{0-inf} (ng · hr/mL)	22798 (26)	99.02	95.5	102.66	22881 (23)	
AUC_{0-1hr} (ng · hr/mL)	1260 (85)	122.71	85.05	177.03	1005 (80)	
AUC_{0-2hr}^b (ng · hr/mL)	3534 (53)	120.52	100.69	144.26	2839 (48)	
AUC_{0-4hr}^c (ng · hr/mL)	8038 (33)	130.54	119.98	142.02	6041 (27)	
AUC_{4hr-t}^d (32)	14707 (32)	86.22	82.35	90.27	16720 (26)	
T_{max} (hr)	1.908 (69)	na	na	na	5.615 (54)	
T_{lag} (hr)	0.236 (106)	na	na	na	0.178 (90)	

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TABLE 18-continued

Acetaminophen Pharmacokinetics (30/500)					
Parameter	Fast Release Formulation				Commercially- available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
T _{1/2} (hr)	4.798 (26)	na	na	na	5.3 (43)
K _{el} (1/hr)	0.153 (25)	na	na	na	0.152 (36)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 19

Acetaminophen Pharmacokinetics (30/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2940 (38)	93.8	84.57	104.03	3085 (29)
C_{1hr} (ng/mL)	2161 (56)	139.29	107.29	180.84	1777 (59)
C_{2hr}^a (ng/mL)	2349 (27)	125.86	113.61	139.44	1892 (28)
AUC_{0-t} (ng · hr/mL)	21822 (26)	99.42	95.9	103.06	21897 (23)
AUC_{0-inf} (ng · hr/mL)	23107 (26)	100.76	97.16	104.49	22881 (23)
AUC_{0-1hr} (ng · hr/mL)	1342 (81)	155.89	107.81	225.4	1005 (80)
AUC_{0-2hr}^b (ng · hr/mL)	3596 (52)	129.14	107.79	154.73	2839 (48)
AUC_{0-4hr}^c (ng · hr/mL)	7880 (32)	130.08	119.51	141.59	6041 (27)
AUC_{4hr-t}^d (ng · hr/mL)	15040 (29)	88.93	84.92	93.13	16720 (26)
T_{max} (hr)	1.724 (62)	na	na	na	5.615 (54)
T_{lag} (hr)	0.19 (114)	na	na	na	0.178 (90)
$T_{1/2}$ (hr)	6.116 (63)	na	na	na	5.3 (43)
K_{el} (1/hr)	.0139 (37)	na	na	na	0.152 (36)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

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TABLE 20

Acetaminophen Pharmacokinetics (30/500)					
Parameter	Slow Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2734 (33)	88.33	79.68	97.91	3085 (29)
C_{1hr} (ng/mL)	1989 (53)	120.26	93.05	155.44	1777 (59)
C_{2hr}^a (ng/mL)	2131 (25)	112.77	101.84	124.86	1892 (28)
AUC_{0-t} (ng · hr/mL)	21272 (23)	97.1	93.68	100.64	21897 (23)
AUC_{0-inf} (ng · hr/mL)	22504 (22)	98.45	94.95	102.07	22881 (23)
AUC_{0-1hr} (ng · hr/mL)	1092 (76)	120.91	84.15	173.72	1005 (80)
AUC_{0-2hr}^b (ng · hr/mL)	3152 (45)	112.74	94.19	134.94	2839 (48)
AUC_{0-4hr}^c (ng · hr/mL)	7217 (26)	119.31	109.5	129.61	6041 (27)
AUC_{4hr-t}^d (26)	15227 (26)	90.59	86.52	94.85	16720 (26)
T_{max} (hr)	1.897 (56)	na	na	na	5.615 (54)
T_{lag} (hr)	0.196 (79)	na	na	na	0.178 (90)
$T_{1/2}$ (hr)	4.843 (27)	na	na	na	5.3 (43)
K_{el} (1/hr)	0.152 (24)	na	na	na	0.152 (36)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^b AUC from zero to the median T_{max} for commercially-available immediate release tablet^c AUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

The pharmacokinetic parameters for the medium release 30/500 formulation and the commercially-available immediate release tablet are shown in Table 21.

TABLE 21

Pharmacokinetic Profile (Mean ± SD) of Oxycodone/APAP versus Commercially-available immediate release tablet (N = 29)						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max} (hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Oxycodone						
30 mg	36.7 ± 10.9	396 ± 116	398 ± 115	4.5 ± 2.3	0.162 ± 0.023	4.4 ± 0.6
OC/500 mg APAP	47.6 ± 12.3*	426 ± 125	430 ± 124	6.9 ± 2.3*	0.164 ± 0.026	4.3 ± 0.6
Acetaminophen						
30 mg	2940 ± 1105	21822 ± 5630	23107 ± 5927	1.7 ± 1.1	0.139 ± 0.052	6.1 ± 3.9
OC/500 mg APAP						

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TABLE 21-continued

Pharmacokinetic Profile (Mean ± SD) of Oxycodone/APAP versus Commercially-available immediate release tablet (N = 29)						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max} (hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Com-mercially-available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	3085 ± 899*	21897 ± 5125	22881 ± 5362	5.6 ± 3.0*	0.152 ± 0.055	5.3 ± 2.3

*Most values occurred after the second dose.

^a AUC and C_{max} dose-normalized to 30 mg for OC and 500 mg for APAP.

Example 4

Clinical Pharmacokinetic Analysis of Controlled-Release 15 mg Oxycodone/650 mg Acetaminophen Bilayer Tablets—Single Dose

The following study evaluated the bioavailability, pharmacokinetics, dose-proportionality, and safety of 1 or 2 tablets of 15 mg of a composition comprising OC/650 mg APAP (1 dose) (see selected example from Chart No. 1) compared to 1 tablet of the commercially-available immediate release tablet under fed conditions. The ER layer contained 75% of the total amount of the oxycodone in the tablet, 50% of the total amount of APAP in the tablet, and 45% (w/w) POLYOX® 1105. The IR layer contained 25% of the total amount of oxycodone in the tablet and 50% of the total amount of APAP. This study was conducted in 42 male and female healthy subjects.

PK parameters for oxycodone are presented in Table 22. Plasma concentrations of OC for the 1 tablet dosing configuration of 15/650 showed a median t_{lag} of 0.25 hours, while there was no lag time for plasma concentrations of OC for the 2 tablet dosing configuration of 15/650 and the commercially-available immediate release tablet under fed conditions. As illustrated in FIG. 9 demonstrating the plasma concentrations of oxycodone versus time of treatment (i.e., Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions; Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions; and Treatment C was one tablet of the commercially-available immediate release tablet (7.5 mg oxycodone/325 mg acetaminophen) administered orally every 6 hours for 2 doses under fed conditions). Plasma concentrations of OC rose rapidly after administration of 15/650 formulation in a similar fashion to commercially-available immediate release tablet. Peak plasma levels of OC for the 15/650 tablets, however, were biphasic. Peak levels were observed at about 2-3 hours and about 6 hours for the 1 or 2 tablet dosing configuration of the 15/650 formulation. In contrast, the peak plasma level of OC for the commercially-available immediate release tablet was about 7-8 hours after the initial dose of the commercially-available immediate release tablet (~1-2 hr after the second dose). Mean plasma concentrations of OC from 15/650 formulations were detectable through 48 hours following all treatments and $t_{1/2}$ was about 4 hours across all treatments.

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TABLE 22

Pharmacokinetic Parameter Estimates (Mean \pm SD) of Oxycodone Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet (N = 25)	17.68 (4.42)	199.60 (59.52)	201.6 (59.27)	3.00 (1.00-12.45)	0.25 (0.00-0.75)	4.18 (0.77)
Treatment A						
Two tablets (N = 25)	29.18 (6.53)	414.73 (109.87)	417.41 ^b (112.17)	5.00 (1.00-12.00)	0.00 (0.00-0.50)	4.11b (0.67)
Treatment B						
Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP (N = 25) Treatment C	20.34 (4.81)	199.63 (60.53)	201.76 (60.24)	7.00 (0.50-9.00)	0.00 (0.00-1.00)	4.08 (0.64)

^a T_{max} and t_{lag} median (minimum-maximum)^bN = 24

PK parameters for APAP are presented in Table 23. Plasma concentrations of APAP for the 1 tablet dosing configuration of 15/650 showed a median t_{lag} of 0.25 hour, while there was no lag in the appearance of APAP in plasma for the 2 tablet dosing configuration of 15/650 and the commercially-available immediate release tablet. Plasma concentrations of APAP rose rapidly after administration of the 15/650 formulations, similar to that observed with RDL. (See FIG. 10). Peak plasma levels of APAP following administration of the 1 tablet and 2 tablet dosing configurations of 15/650 were observed at approximately 2 hours (with a shoulder peak at 5-6 hours) after dosing compared with 1 hour after the second dose of the commercially-available immediate release tablet. Mean plasma concentrations of APAP were detectable through 36 hours following all treatments and the mean $t_{1/2}$ was approximately 6 to 8 hours across treatment groups.

Example 5

Clinical Pharmacokinetic Analysis of Controlled-Release 15 mg Oxycodone/650 mg Acetaminophen Bilayer Tablets—Multiple Doses

The following study evaluated the steady state bioavailability, pharmacokinetics, and safety of a 15 mg OC/650 mg APAP composition administered (see selected example from Chart No. 2) orally as 1 tablet (Treatment A) or 2 tablets (Treatment B) every 12 hours (9 doses) compared to 2 tablets of the commercially-available immediate release tablet (2 \times 7.5 mg OC/325 mg APAP) (Treatment C) dosed every 6 hours for 4.5 days (18 doses) under fed conditions with 48 male and female subjects in equal distribution.

TABLE 23

Pharmacokinetic Parameter Estimates (Mean \pm SD) of APAP Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet (N = 25)	3822 (874)	30239 (5673)	32194 ^c (6437)	2.00 (0.50-4.00)	0.25 (0.00-1.00)	6.17 ^c (2.22)
Two tablets (N = 25)	6941 (1989)	64783 (15017)	67600 ^d (14655)	2.00 (0.50-5.00)	0.00 (0.00-0.50)	7.67 ^d (4.06)
Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP (N = 25)	3629 (841)	30137 (6426)	30802 ^c (6697)	6.50 (0.50-9.00)	0.00 (0.00-1.00)	5.89 ^c (2.63)

^a T_{max} and t_{lag} median (minimum-maximum)^cN = 21^dN = 23

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The pharmacokinetic (PK) parameters of OC are presented in Table 24. The PK behavior of OC on Study Day 1 was similar to that observed in the single dose study (see Table 22). There was a slight lag (median lag 0.25 hr) in the appearance of OC following the 1 tablet dose of 15 mg OC/650 mg APAP. No lag was observed following dosing with 2 tablets of 15 mg OC/650 mg APAP or the commercially-available immediate release tablet. Peak plasma levels were observed at 4 and 6 hours after administration of 1 and 2 tablets of the 15/650 formulation, respectively, and at 1.5 hours after the second dose of the commercially-available immediate release tablet. (See FIG. 11). Minimum (trough) plasma concentrations (C_{min}) of OC achieved steady-state levels by Day 2 for 15/650 formulations and by Day 3 for the commercially-available immediate release tablet.

TABLE 24

Oxycodone Pharmacokinetic Parameters					
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
A: One tablet Day 1 (N = 20)	18.79 (5.00)	149.68 ^c (37.92)	4.00 (2.00- 8.00)	0.25 (0.00- 0.50)	Day 1
B: Two tablets Day 1 (N = 20)	33.57 (8.41)	280.45 ^c (62.61)	5.93 (1.00- 11.92)	0.00 (0.00- 0.25)	Day 1
C: Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP Day 1 (N = 20)	36.02 (10.52)	278.60 ^c (67.17)	7.50 (0.75- 11.92)	0.00 (0.00- 0.33)	Day 1
A: One tablet Day 5 (N = 20)	27.26 (6.33)	223.10 ^c (59.45)	3.00 (1.00- 5.92)	Day 5	6.06 ^d (1.91)
B: Two tablets Day 5 (N = 20)	50.70 (10.95)	433.37 ^c (93.21)	3.00 (2.00- 7.00)	Day 5	6.35 (1.89)
C: Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP Day 5 (N = 20)	52.41 (12.40)	435.70 ^c (98.68)	2.00 (0.50- 8.02)	Day 5	5.93 ^d (1.68)

^a T_{max} and t_{lag} median (minimum-maximum)^cDay 1 - AUC_{0-12h} ; Day 5 - AUC_{0-12h}^{ss} ^dN = 19

On Day 5 of the study, the maximum plasma OC concentration at steady-state (C_{max}^{ss}) was 27.3 ng/mL following 4.5 days of dosing with 1 tablet of 15 mg OC/650 mg APAP administered every 12 hours. C_{max}^{ss} following 2 tablets of 15 mg OC/650 mg APAP administered every 12 hours or the commercially-available immediate release tablet administered Q6 hours for 4.5 days were 50.7 ng/mL and 52.4 ng/mL, respectively. Median T_{max}^{ss} was observed at 3 hours following 1 tablet or 2 tablets of 15/650 and at 2 hours following the first daily dose of the commercially-available immediate release tablet.

PK parameters for APAP are presented in Table 25. Acetaminophen was rapidly absorbed following a single dose of 1 or 2 tablets of 15/650 and in a similar fashion to the commercially-available immediate release tablet (see FIG. 12). There was no lag in plasma concentrations following any of the three dosing regimens. Peak APAP plasma concentrations were observed at 1 hour after administration of 1 or 2 tablets of 15/650 and at 0.9 hours after the first dose of the commercially-available immediate release tablet on Day 1. After a single administration of 15/650, C_{max} for APAP was proportional with respect to the amount of APAP in 1 or 2

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tablets of 15/650 (i.e., 1 tablet—3942 ng/mL; 2 tablets—7536 ng/mL). Minimum (trough) concentrations (C_{min}) of APAP achieved steady-state levels by Day 2 for 1 tablet of 15/650, by Day 4 for 2 tablets of 15/650 and by the second dose on Day 1 for the commercially-available immediate release tablet.

TABLE 25

Acetaminophen Pharmacokinetic Parameters					
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
A: One tablet Day 1 (N = 20)	3942 (1168)	22928 ^c (7331)	1.00 (0.50- 5.93)	0.00 (0.00- 0.28)	Day 1
B: Two tablets Day 1 (N = 20)	7536 (2205)	44254 ^c (13885)	1.00 (0.28- 4.00)	0.00 (0.00- 0.25)	Day 1
C: Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP Day 1 (N = 20)	6757 (1949)	43634 ^c (12357)	0.90 (0.32- 11.92)	0.00 (0.00- 0.25)	Day 1
A: One tablet Day 5 (N = 20)	4635 (1330)	26968 ^c (9134)	1.00 (0.50- 3.00)	Day 5	7.06 (2.24)
B: Two tablets Day 5 (N = 20)	8206 (2666)	50221 ^c (18415)	1.00 (0.30- 4.00)	Day 5	7.46 (1.85)
C: Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP Day 5 (N = 20)	7433 (1979)	50678 ^c (15565)	1.50 (0.25- 8.02)	Day 5	6.79 ^b (2.47)

^a T_{max} and t_{lag} median (minimum-maximum)^cDay 1 - AUC_{0-12h} ; Day 5 - AUC_{0-12h}^{ss} ^bN = 17

On Day 5 of the study, median T_{max}^{ss} for APAP was observed at 1 hour following 1 or 2 tablets of 15/650 and at 1.5 hours following the first daily dose of the commercially-available immediate release tablet on Day 5. Maximum plasma APAP concentration at steady-state (C_{max}^{ss}) was 4635 ng/mL following 4.5 days of dosing with 1 tablet of 15/650 every 12 hours (Table 25). C_{max}^{ss} following 2 tablets of 15/650 administered every 12 hours and for the commercially-available immediate release tablet administered Q6 hours for 4.5 days were 8206 and 7433 ng/mL, respectively.

Example 6

Clinical Pharmacokinetic Analysis of Controlled-Release 15 mg Oxycodone/650 mg Acetaminophen Bilayer Tablets Under Fed and Fasted Conditions

Two open-label, randomized, two-period crossover studies were conducted to evaluate the effect of food on the pharmacokinetics, bioavailability and safety of the 15 mg oxycodone/650 mg APAP composition (see selected example from Chart No. 2) using a 1 tablet or 2 tablet dosing configuration in normal, healthy subjects. Studies were conducted in 48 subjects under fed (FDA high fat breakfast) or fasted conditions.

Tables 26 and 27 present the pharmacokinetic data for oxycodone (OC) and APAP, respectively. FIGS. 13 and 14 present the plasma concentration of OC following administration of one tablet and two tablets, respectively, under fed (Treatment A) or fasted (Treatment B) conditions. FIGS. 15 and 16 present the plasma concentration of APAP following administration of one tablet and two tablets, respectively, under fed (Treatment A) or fasted (Treatment B) conditions.

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TABLE 26

Oxycodone Pharmacokinetics (15/650)							
Dose	State (N)	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max}^a (hr)	t_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet	fed (28)	19.03 (4.20)	219.23 (55.99)	221.06 (55.88)	5.00 (1.00-12.00)	0.25 (0.00-0.50)	3.94 (0.69)
Two tablets	fed (17)	30.58 (6.57)	414.01 (104.76)	415.88 (104.86)	5.00 (0.75-12.00)	0.25 (0.00-0.27)	4.42 (0.97)
One tablet	fasted (28)	18.31 (4.67)	196.51 (53.04)	198.33 (52.82)	3.50 (0.50-10.00)	0.00 (0.00-0.25)	4.25 (0.59)
Two tablets	fasted (17)	33.69 (7.45)	390.33 (145.27)	392.15 (145.81)	5.00 (2.00-5.20)	0.00 (0.00-0.25)	4.80 (1.07)

^a T_{max} and t_{lag} median (minimum-maximum)

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Plasma concentrations (Table 26; FIGS. 13 and 14) of OC rose rapidly with the median T_{max} observed at about 4 to 5 hr under both fed and fasted conditions for both the 1- and 2-tablet dose configurations. OC plasma levels were biphasic—with a first peak at about 3 hours and a second peak at about 5 hours. The C_{max} values (at 5 hours) for OC under fed (1 and 2 tablets, 19.0 and 30.6 ng/mL) conditions were equivalent to those observed under fasted (1 and 2 tablets, 18.3 and 33.7 ng/mL) conditions for both the 1 tablet and 2 tablet dosing configurations.

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concentration in the plasma of the user. Basic science and clinical observation suggest that a shortened time to maximum plasma concentration (t_{max}) and a heightened maximum plasma concentration (C_{max}) would increase the euphoric effects conferred by a drug. The abuse quotient (AQ) is a relatively new concept that attempts to predict the abuse potential of drugs. The AQ refers to the two PK parameters expressed as a ratio: $AQ = C_{max}/t_{max}$. The abuse potential of a drug increases as the value of the AQ increases, either by heightening C_{max} or shortening t_{max} .

TABLE 27

Acetaminophen Pharmacokinetics (15/650)							
Dose	State (N)	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max}^a (hr)	t_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet	fed (28)	4374 (1286)	31480 (9316)	32552 (9489)	1.00 (0.50, 5.00)	0.00 (0.00-0.50)	4.65 (1.26)
Two tablets	fed (17)	6341 (1698)	62904 (19294)	68839 ^b (19826)	2.00 (0.75-6.00)	0.00 (0.00-0.25)	7.02 ^b (1.77)
One tablet	fasted (28)	5511 (2095)	31876 (103339)	33860 (10731)	0.75 (0.25, 5.00)	0.00 (0.00-0.25)	5.19 ^c (1.50)
Two tablets	fasted (17)	10428 (3529)	61164 (16552)	65281 (15711)	0.75 (0.25-5.00)	0.00 (0.00-0.00)	5.6 (1.49)

^a T_{max} and t_{lag} median (minimum-maximum)^bN = 12^cN = 27^dN = 13

Plasma concentrations (Table 27; FIGS. 15 and 16) of APAP rose rapidly following 1 tablet dosed under fed and fasted conditions with similar T_{max} values (1.0 hour and 0.8 hour). T_{max} was observed sooner following 2 tablets given under fasted conditions (0.8 hour) than under fed conditions (2 hours). Plasma concentrations of APAP were lower under fed conditions than under fasted conditions with fed C_{max} values of 4374 ng/mL (1 tablet) and 6341 ng/mL (2 tablets) and fasted C_{max} values of 5511 ng/mL (1 tablet) and 10,428 ng/mL (2 tablets). Nevertheless, the peak concentrations demonstrate that there was only a slight, minimal food effect on the absorption of APAP, which is consistent with that observed for other oxycodone and acetaminophen products. Thus, there is no meaningful food effect seen with this composition, and as such, the composition can be administered without regard to food.

Example 7

Abuse Potential of Controlled-Release Formulations

It has long been theorized that the desirability of a drug of abuse is related to the speed with which it reaches maximum

Table 28 presents the AQs for various extended release formulations disclosed herein (see, e.g., selected examples from Chart Nos. 1 and 2) and several commercially available formulations.

TABLE 28

Abuse Quotient			
Formulation	C_{max} (ng/mL)	t_{max} (hr)	AQ
15/500 - Fast	18.8	4.95	3.80
15/500 - Medium	18.27	5.31	3.44
15/500 - Slow	17.4	5.66	3.07
15/650 - 1 tablet	17.68	3.90	4.53
15/650 - 2 tablets	14.59*	5.03	2.90
7.5/325 - 1 tablet	16.82	3.71	4.53
7.5/325 - 2 tablets	16.39	3.17	5.17
Percocet	22.43	2.16	10.38
Oxycontin	17.35	3.54	4.90
OxyER	19.61	4.11	4.77

*dose normalized to 15 mg

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Example 8

Ethanol Release Testing at a 150 rpm Paddle Speed

To assess the potential for dose dumping, the in vitro dissolution of oxycodone and APAP from 7.5 mg OC/325 mg APAP tablets was tested in 0.1 N HCl containing 0%, 5%, 20%, or 40% v/v ethanol. The ER layer of the 7.5/325 tablets contained 5.625 mg of OC, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105, and the IR layer contained 1.875 mg of OC and 162.5 mg of APAP. (See selected example from Chart No. 1.) For each profile, twelve tablets were weighed, placed in a sinker, and dropped into an equilibrated USP Type II apparatus (paddles) that contained 900 mL of (helium sparged) 0.1 N HCl (containing either 0%, 5%, 20%, or 40% ethanol) heated to 37° C. The mixture was stirred at ~150 rpm

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TABLE 30

Percent Release in 5% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	31.2	2.4	30.2	32.4	52.1	1.5	50.5	53.5
30	36.9	3.2	35.1	39.0	54.9	1.6	53.4	56.4
45	41.5	3.3	39.1	44.0	57.2	1.5	55.7	58.7
60	45.5	3.5	43.4	48.2	59.4	1.5	57.9	60.9
75	49.4	2.6	47.9	52.5	61.5	1.5	60.0	63.0
90	52.9	3.5	50.7	56.1	63.4	1.5	61.9	65.0
105	56.2	1.8	54.0	57.8	65.4	1.5	63.8	66.9
120	59.3	2.8	56.7	61.7	67.2	1.5	65.6	68.7

TABLE 31

Percent Release in 20% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Minimum	Maximum	Mean	RSD	Minimum	Maximum
15	28.5	4.1	26.5	30.3	51.3	2.9	48.2	53.1
30	33.6	3.3	32.3	35.7	54.1	2.3	51.3	55.7
45	38.3	2.8	35.7	39.9	56.3	2.2	53.7	58.0
60	41.8	3.6	38.1	44.1	58.3	2.1	55.6	59.9
75	45.6	3.0	43.4	48.8	60.2	2.0	57.7	61.8
90	48.7	3.3	46.1	52.0	62.0	2.0	59.4	63.6
105	51.4	3.0	49.1	53.7	63.7	1.9	61.1	65.2
120	54.3	2.7	51.3	56.7	65.4	1.9	62.9	66.8

and the temperature was maintained at 37° C. for 120 minutes. The bath vessel was covered with a low evaporation vessel cover. Samples were removed at 15, 30, 45, 60, 75, 90, 105, and 120 minutes. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

Tables 29, 30, 31, and 32 present the percent release of OC and APAP in the presence of 0%, 5%, 20%, and 40% ethanol, respectively. FIG. 17 presents dissolution profiles for OC and FIG. 18 presents dissolution profiles for APAP in the presence of 0%, 5%, 20%, and 40% ethanol. These data reveal that for both OC and APAP, the dissolution in 5%, 20%, or 40% ethanol was either comparable or slower than the dissolution in 0% ethanol, indicating no dose dumping for this formulation.

TABLE 29

Percent Release in 0% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	32.0	2.7	31.1	33.4	52.9	2.7	50.6	56.0
30	37.6	2.4	36.5	39.2	55.6	2.5	53.5	58.6
45	42.3	2.6	40.9	44.4	58.1	2.5	56.0	61.1
60	46.5	2.5	45.0	48.7	60.5	2.4	58.4	63.5
75	50.4	2.5	48.7	52.5	62.9	2.4	60.8	65.9
90	54.1	2.4	52.1	56.2	65.0	2.3	62.9	68.0
105	57.7	2.1	55.6	59.8	67.1	2.3	65.0	70.1
120	61.1	2.2	58.9	63.5	69.1	2.2	66.9	72.1

TABLE 32

Percent Release in 40% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	10.3	16.3	7.8	13.7	20.7	16.3	15.8	25.9
30	20.7	8.6	16.5	23.0	37.1	7.7	31.4	41.4
45	28.6	10.4	24.4	33.4	44.4	2.6	42.2	45.8
60	31.3	5.9	29.2	35.0	47.0	1.4	45.9	48.0
75	34.5	6.5	30.3	38.1	49.0	1.4	47.7	49.8
90	36.8	7.0	33.9	41.2	50.5	1.5	49.2	51.6
105	38.5	6.8	35.3	44.0	51.9	1.7	50.4	53.1
120	40.7	4.5	38.0	43.5	53.2	1.4	51.5	54.1

Example 9

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of Oxycodone/Acetaminophen Administered Under Fed and Fasted Conditions

An open-label, randomized, three-period crossover study was conducted to evaluate the pharmacokinetics (PK), bioavailability, and safety of two tablets of a multi-layer extended-release formulation (each tablet comprising 7.5 mg oxycodone hydrochloride/325 mg acetaminophen), administered as a single dose in normal, healthy subjects under fed (high-fat or low-fat meal) and fasted conditions (i.e., 10 hr fast).

This single center, open-label, randomized, 3-period, 6-sequence crossover study in normal, healthy subjects was designed to evaluate the effect of a high-fat and low-fat meal on the PK, bioavailability, and safety of a multilayer ER tablet

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formulation of 7.5 mg OC/325 mg APAP (see selected example from Chart No. 1). The formulation was orally administered as 2 tablets (15 mg OC/650 mg APAP total dose) under 2 types of fed (high-fat and low-fat) and fasted conditions. Forty-eight subjects were enrolled and 31 subjects completed the study. Only subjects that completed all 3 study periods have been included in the PK evaluation.

Following a 10 hour overnight fast, subjects randomized to Treatment A consumed an entire standardized FDA high-fat breakfast (approximately 1,000±100 calories and approximately 50% from fat); those receiving Treatment B consumed an entire low-fat breakfast (approximately 800±80 calories and approximately 25% to 30% from fat). Breakfasts were consumed within 30 minutes prior to Hour 0 study drug administration. Subjects who could not consume the entire breakfast in the allotted time were dropped from the study. Subjects randomized to Treatment C were administered study drug under fasted conditions following an overnight fast of at least 10 hours. No food was allowed for the first 4 hours postdose. Blood samples were collected pre-dose (up to 60 minutes prior to dose), and at 15 min, 30 min, 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36 and 48 hours post-dose, and the resulting plasma samples were analyzed for OC and APAP using a validated liquid chromatography-tandem mass spectrometry assay with a linear range of 0.100 to 100 ng/mL for OC and 100 to 50,000 ng/mL for APAP. Pharmacokinetic parameters, as detailed above in Example 2, were determined.

Tables 33 and 34 presents PK parameters for OC under the three treatment conditions, and FIG. 19 presents plasma OC concentration-time profiles for the treatments. Mean plasma concentration profiles of OC revealed that OC was rapidly absorbed under both fed (high and low fat meal) and fasted conditions. There was a slight lag (median 0.25 hours) when the formulation was administered after a meal (high and low fat). The median of the time of observed maximum plasma concentrations (T_{max}) were 4 hours and 3 hours after administration under low fat and fasted conditions, respectively. Median T_{max} for OC under high fat conditions was significantly delayed, as compared to fasted conditions (5 hr vs. 3 hr; $P<0.05$). Average maximum plasma OC concentrations (C_{max}) were 19.94 ng/mL after a low fat breakfast, 17.90 ng/mL after a high fat breakfast, and 15.91 ng/mL under fasted conditions.

TABLE 33

Oxycodone Pharmacokinetic Estimates (2 tablets of 7.5/325)			
Parameter	Treatment A High Fat	Treatment B Low Fat	Treatment C Fasted
	Mean (SD) (N = 31)	Mean (SD) (N = 31)	Mean (SD) (N = 31)
$AUC_{0-\infty}$ (ng · hr/mL)	219.41 (54.07)	219.49 (57.29)	190.70 (50.03)
AUC_{0-48} (ng · hr/mL)	221.00 (54.14)	221.38 (56.95)	192.63 (49.69)
C_{max} (ng/mL)	17.90 (4.25)	19.94 (4.66)	15.91 (3.43)
T_{max} (h) ^a	5.00 (1.00-12.00)	4.00 (1.00-5.00)	3.00 (0.75-8.00)
K_{el} (1/h)	0.1682 (0.0298)	0.1693 (0.0321)	0.1502 (0.0269)
t_{lag} (h) ^a	0.25 (0.00-1.00)	0.25 (0.00-0.75)	0.00 (0.00-0.25)
$t_{1/2}$ (h)	4.26 (0.83)	4.26 (0.91)	4.76 (0.87)

^aMedian (minimum-maximum).

A comparison of C_{max} showed that OC concentrations were 12% and 25% higher when the formulation was given under high fat (Treatment A) and low fat (Treatment B) conditions, compared to fasted conditions (Treatment C; see

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Table 33). The C_{max} for Treatment A was bioequivalent to both Treatments B (84%-96%) and C (105%-120%) as the 90% CIs for the geometric ratios were contained within 80% to 125% (see Table 34). The C_{max} observed for Treatment B was not bioequivalent to Treatment C (117%-134%). AUCs were approximately 15% higher when the formulation was administered under fed conditions (high and low fat), as compared to fasted conditions (Table 33). AUC for both Treatments A and B (high fat and low fat) were bioequivalent to Treatment C (fasted; 111%-121% and 111%-120% for AUC_{0-t} and 111%-120% and 110%-120% for $AUC_{0-\infty}$) (Table 34). The apparent plasma terminal elimination half-life ($t_{1/2}$) for OC was similar when the formulation was administered under fed (4 hours) and fasted conditions (5 hours).

TABLE 34

Oxycodone Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment A/C Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment A/B Fed (High Fat)/ Fed (Low Fat)
$AUC_{0-\infty}$ (ng · hr/mL) ^a	115.41 (110.63, 120.41)	115.09 (110.38, 120.01)	100.28 (96.18, 104.55)
AUC_{0-t} (ng · hr/mL) ^a	115.85 (111.00, 120.90)	115.30 (110.54, 120.27)	100.47 (96.34, 104.79)
C_{max} (ng/mL) ^a	112.11 (104.61, 120.16)	125.16 (116.88, 134.03)	89.57 (83.67, 95.90)

^aN = 31.

PK parameters for APAP are presented in Tables 35 and 36 and the plasma APAP concentration-time profiles are presented in FIG. 20. APAP was rapidly absorbed following administration under fed (high and low fat meals) and fasted conditions. There was a slight lag when the formulation was administered after a low fat breakfast (median lag time [t_{lag}] 0.25 hours). There was no lag in the absorption of APAP when administered following a high fast breakfast or after fasting. The time to C_{max} was significantly ($P<0.05$) longer when administered after a meal (high and low fat; median $T_{max}=2$ hours) than when administered under fasted conditions (median $T_{max}=0.5$ hour). Average C_{max} values for APAP were lower after a high (3,775 ng/mL) and low fat (3,863 ng/mL) meal than when administered under fasted conditions (5,175 ng/mL). Geometric mean ratios for C_{max} following Treatments A and B were 24% to 23% lower than for Treatment C (Table 36). The 90% CIs for C_{max} following Treatment A (70%-82%) and Treatment B (72%-83%) with reference to fasted state were outside the bioequivalent range of 80%-125%. The AUCs for APAP were almost identical when the formulation was administered under high fat, low fat, or fasted conditions. (Comparison of geometric mean ratios of AUC_{0-t} and $AUC_{0-\infty}$ for Treatments A (90% CI 97%-103% and 96%-102%) and B (90% CI 96%-101% and 94% to 100%) with those for Treatment C showed that treatments were bioequivalent. The $t_{1/2}$ for APAP after the formulation was administered after a high or low fat meal (5 hours) was slightly shorter than when administered under fasted conditions (7 hours).

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TABLE 35

APAP Pharmacokinetic Estimates (2 tablets of 7.5/325)			
Parameter	Treatment A Fed (High Fat) Mean (SD) (N = 31)	Treatment B Fed (Low Fat) Mean (SD) (N = 31)	Treatment C Fasted Mean (SD) (N = 31)
AUC _{0-t} (ng · hr/mL)	29617.96 (7765.99)	29346.82 (7869.75)	29763.19 (7592.89)
AUC _{0-∞} (ng · hr/mL)	31457.06 (7973.16) ^a	30550.48 (8051.47)	31807.70 (7923.30) ^a
C _{max} (ng/mL)	3774.52 (949.84)	3862.90 (978.08)	5175.48 (1731.31)
T _{max} (h) ^b	2.00 (0.50-5.00)	2.00 (0.50-5.00)	0.53 (0.23-5.00)
K _{el} (1/h)	0.1564 (0.0363) ^a	0.1593 (0.0408)	0.1146 (0.0360) ^a
t _{lag} (h) ^b	0.00 (0.00-1.00)	0.25 (0.00-0.50)	0.00 (0.00-0.25)
t _{1/2} (h)	4.66 (1.08) ^a	4.71 (1.60)	6.63 (1.99) ^a

^aN = 29^bMedian (minimum-maximum).

TABLE 36

APAP Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment A/C Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment A/B Fed (High Fat)/ Fed (Low Fat)
AUC _{0-∞} (ng · hr/mL) ^a	98.60 (95.75, 101.54)	96.56 (93.80, 99.39)	102.12 (99.20, 105.11)
AUC _{0-t} (ng · hr/mL) ^b	99.88 (97.31, 102.52)	98.79 (96.27, 101.37)	101.10 (98.54, 103.74)
C _{max} (ng/mL) ^b	76.00 (70.49, 81.94)	77.18 (71.65, 83.13)	98.48 (91.45, 106.05)

^aN = 27^bN = 31.

In summary, total exposure (AUC) for OC was slightly increased (by about 15%) when the formulation was administered with food (after high- or low-fat meal); however, AUCs for OC were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted and high fat vs. low fat). Peak exposure (C_{max}) for OC was 12% and 25% higher under high fat and low-fat conditions, respectively, compared to fasted conditions. The C_{max} for OC after a high-fat meal was bioequivalent to fasted conditions, as well as to low fat conditions, whereas the C_{max} under low fat conditions was not

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equivalent to those under fasted conditions. The AUCs for APAP were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted, and high fat vs. low fat). The peak exposure (C_{max}) for APAP was decreased by about 24% in fed (high- and low-fat) states as compared to the fasted state.

Example 10

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Oxycodone/325 mg Acetaminophen—Single Dose

An open-label, randomized, 3-period crossover study was performed to evaluate the single dose pharmacokinetic (PK) parameters, bioavailability, and safety of an extended-release formulation containing 7.5 mg OC/325 mg APAP (see selected example from Chart No. 1) in healthy subjects under fasted conditions. The PK and bioavailability of the extended-release formulation administered as 1 or 2 tablets were compared to the commercially-available immediate release tablet (immediate release 7.5 mg OC/325 mg APAP) administered as 1 or 2 tablets every 6 hours for 2 doses. This study was conducted in 48 male and female subjects, with equal gender distribution.

Pharmacokinetic parameter estimates for OC are presented in Table 37, and OC plasma concentration-time profiles are presented in FIG. 21. There was no lag in absorption of OC for the 1 and 2 tablet dosing configurations of the extended release formulation and the commercially-available immediate release tablet under fasted conditions. Plasma concentrations of OC rose rapidly after administration of the extended release formulation in a similar fashion to the commercially-available immediate release tablet, and peak plasma levels of OC were observed (T_{max}) at 4 and 3 hours for the 1 or 2 tablet dosing configuration of the extended release formulation compared with 7 hours after the initial dose of 1 tablet of the commercially-available immediate release tablet (1 hour after the second dose) and 0.75 hours after the initial dose of 2 tablets of the commercially-available immediate release tablet. Mean plasma concentrations of OC from the extended release formulation were detectable through 36 hours in most subjects following all treatments and t_{1/2} was about 4 to 5 hours across all treatments. The extent of exposure (AUC_{0- t} and AUC_{0- ∞}) for the 2 tablet dosing configuration of the extended release formulation increased proportionally with dose compared with the 1-tablet dosing configuration of the extended release formulation.

TABLE 37

Oxycodone Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
AUC _{0-t} (ng · hr/mL)	87.43 (24.59)	185.98 (47.64)	191.15 (53.43)	401.23 (110.56)
AUC _{0-∞} (ng · hr/mL)	89.85 (24.73) ^b	187.71 (47.58)	193.10 (53.22)	403.04 (110.45)
C _{max} (ng/mL)	8.41 (2.06)	16.39 (4.31)	20.82 (5.98)	41.24 (12.12)
T _{max} (h) ^a	4.00 (0.75-5.92)	3.00 (0.75-6.50)	7.38 (0.50-10.00)	0.75 (0.50-12.00)
t _{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.52)	0.00 (0.00-0.25)	0.00 (0.00-0.25)
t _{1/2} (h)	4.50 (0.78) ^b	4.87 (0.93)	4.08 (0.89)	4.34 (1.02)
K _{el} (h ⁻¹)	0.1590 (0.0307) ^b	0.1473 (0.0274)	0.1770 (0.0352)	0.1688 (0.0415)

^aMedian (minimum-maximum).^bN = 32

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No dose-dumping was observed in any subject receiving the ER formulation. The interindividual variability (CV %) for C_{max} of OC after administration of 1 or 2 tablets of the ER formulation was comparable to 1 tablet of the commercially-available immediate release tablet and less than 29% for all 3 treatments. Similarly the interindividual variability (CV %) for AUC of OC was 28% or less for 1 and 2 tablets of the ER formulation and 1 tablet of the commercially-available immediate release tablet.

Table 38 presents APAP PK parameter estimates and FIG. 22 presents APAP plasma concentration-time profiles. The appearance of plasma concentrations of APAP for all dose configurations of the extended release formulation and the commercially-available immediate release tablet showed no lag. Plasma concentrations of APAP rose rapidly after administration of the extended release formulation, similar to that observed with the commercially-available immediate release tablet. Peak plasma levels of APAP following administration of the 1 tablet and 2 tablet dosing configurations of the extended release formulation were observed (median T_{max}) at 0.75 hours after dosing compared with 0.5 hours after the first dose of the commercially-available immediate release tablet (1 and 2 tablets). Mean plasma concentrations of APAP were detectable through 36 hours following all treatments and the mean $t_{1/2}$ was approximately 4 to 7 hours across treatment groups. The extent of exposure (AUC) to APAP following dosing with 1 and 2 tablets of the extended release formulation increased proportionally with dose.

TABLE 38

APAP Pharmacokinetic Estimates (7.5/325)

Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
AUC _{0-t} (ng · hr/mL)	15871 (4841)	32665 (10894)	33040 (9589)	69837 (22945)
AUC _{0-inf} (ng · hr/mL)	16995 (5073)	34836 (11067) ^b	34236 (10126) ^b	71949 (24234) ^c
C_{max} (ng/mL)	2632 (918)	5230 (2086)	4878 (1545)	10741(4123)
T_{max} (h) ^a	0.75 (0.25-2.02)	0.75 (0.25-4.00)	0.50 (0.25-9.00)	0.50 (0.25-12.00)
t_{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.25)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
$t_{1/2}$ (h)	5.33 (1.53)	6.88 (2.15) ⁶	4.41 (1.16) ^b	5.76 (1.47) ^c
K_{el} (h ⁻¹)	0.1421 (0.0479)	0.1103 (0.0337) ^b	0.1669 (0.0411) ^b	0.1291 (0.0368) ^c

^aMedian (minimum-maximum).^bN = 32^cN = 25

No dose-dumping was observed in any subject receiving the ER formulation. The interindividual variability (CV %) for C_{max} of APAP was slightly more after administration of 1 and 2 tablets of the ER formulation (35% and 40%, respectively) than for 1 tablet of the commercially-available immediate release tablet (32%). The interindividual variability (CV %) for AUC of APAP was less than 33% for all 3 treatments.

Both OC and APAP were rapidly absorbed under all conditions with no lag in plasma concentrations. Both OC and APAP levels were sufficiently high within 1 hour after administration of the extended release formulation. Peak exposure to OC was 18% to 21% lower for the ER formulation than for the commercially-available immediate release tablet (1 tablet Q6h). OC levels were sustained over the proposed 12 h dosing

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interval. By 12 hours after dosing with the extended release formulation, APAP plasma levels were less than 20% of C_{max} . Total exposure to both OC and APAP from the extended release formulation was equivalent to that of 1 tablet of the commercially-available immediate release tablet.

To further analyze the absorption of OC and APAP from the ER formulation, the plasma concentrations of OC and APAP following administration of 1 tablet of the ER formulation, 2 tablets of the ER formulation, and the commercially-available immediate release tablet were deconvolved using WinNonlin 5.2 (Pharsight). Deconvolution evaluates in vivo drug release and delivery based on data for a known drug input. Depending upon the type of reference input information available, the drug transport evaluated will be either a simple in vivo drug release (e.g., gastro-intestinal release) or a composite form, typically consisting of an in vivo release followed by a drug delivery to the general systemic circulation. It can estimate the cumulative amount and fraction absorbed over time for the subjects, given PK profile data and dose. For a pure immediate release (IR) or an extended release (ER) formulation the cumulative absorption plot shows a monoexponential curve whereas for a bilayer formulation (IR+ER) a biexponential (rapid phase followed by slower phase) absorption curve will be observed. FIG. 23 and FIG. 24 present the deconvolution plots for OC and APAP, respectively. For each, there is an early rapid phase of absorption that is followed by a later slower phase of absorption from the ER formulation.

Example 11

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Oxycodone/325 mg Acetaminophen—Multiple Doses

An open-label, randomized, 3-period crossover study was performed to evaluate the steady-state PK, bioavailability, and safety of the extended release formulation containing 7.5 mg OC/325 mg APAP in healthy subjects (see selected example from Chart No. 1). The PK and bioavailability of the ER formulation administered as 1 or 2 tablets every 12 hours for 4.5 days (9 doses) was compared to the commercially-available immediate release tablet (immediate release 7.5 mg OC/325 mg APAP) administered as 1 tablet every 6 hours for 4.5 days (18 doses) under fasted conditions (10 hours for the

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first dose on Days 1 and 5; at least 1 hour for all other doses). This study was conducted in 48 male and female subjects, with equal gender distribution.

The PK behavior of OC on Study Day 1 (see Table 39) was similar to that observed in the single dose study (see Example 10). There was no lag (median t_{lag} 0 hours) in the absorption of OC following administration of the ER formulation (1 or 2 tablets) and the commercially-available immediate release tablet, and no dose-dumping was observed for any subject. Peak plasma levels were observed at 3 hours after administration of 1 and 2 tablets of the ER formulation and at 1 hour after the second dose of the commercially-available immediate release tablet (FIG. 25). On Day 1, interindividual variability (% CV) in the C_{max} for OC was slightly higher for 1 tablet (29%) than for 2 tablets (23%) of the ER formulation or the commercially-available immediate release tablet (up to 22%). The variability in the AUC_{0-12h} for OC was comparable between all 3 treatments (21% to 23%). Minimum (trough) plasma concentrations (C_{min}) of OC achieved steady-state levels by Day 4 for 1 tablet of the ER formulation and the commercially-available immediate release tablet and by Day 3 for 2 tablets of the ER formulation. Trough levels of OC on Days 2 through 5 for 2 tablets of the ER formulation were comparable to those observed for the commercially-available immediate release tablet.

TABLE 39

Oxycodone Pharmacokinetic Estimates - Day 1			
Parameter	Treatment A	Treatment B	Treatment C
	ER Formulation	ER Formulation	Commercially-available immediate release tablet
	(1 Tablet Q12h)	(2 Tablets Q12h)	(1 Tablet Q6h)
	Mean (SD)	Mean (SD)	Mean (SD)
	(N = 33)	(N = 33)	(N = 33)
AUC_{0-12h}	66.93 (15.14)	135.89 (30.81)	141.73 (29.78)
(ng · hr/mL)			
C_{max} (ng/mL)	8.34 (2.37)	17.05 (3.97)	21.93 (4.80)
T_{max} (h) ^a	3.00 (0.75-7.00)	3.00 (0.50-5.92)	7.00 (0.50-8.00)
t_{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.32)	0.00 (0.00-0.25)

^aMedian (minimum-maximum).

On Day 5 (see Table 40), steady state was achieved and the median T_{max}^{ss} was observed at 2 hours following 1 tablet or 2 tablets of the ER formulation and at 30 min following the second daily dose of the commercially-available immediate release tablet. Maximum observed plasma concentrations at steady-state (C_{max}^{ss}) for OC for the 1 and 2 tablet dosing configurations of the ER formulation were not equivalent to the commercially-available immediate release tablet. On Day 5, interindividual variability (% CV) in C_{max}^{ss} and AUC_{0-12h}^{ss} for OC was comparable between all 3 treatments (up to 29%). The degree of fluctuation (DFL) in and the swing of plasma concentrations for the ER formulation over the last 12 hour dosing interval on Day 5 were 15% to 22% less than that observed for the commercially-available immediate release tablet.

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TABLE 40

Oxycodone Pharmacokinetic Estimates - Day 5			
Parameter	Treatment A	Treatment B	Treatment C
	ER Formulation	ER Formulation	Commercially-available immediate release tablet
	(1 Tablet Q12 h)	(2 Tablets Q12 h)	(1 Tablet Q6 h)
	Mean (SD)	Mean (SD)	Mean (SD)
	(N = 33)	(N = 33)	(N = 33)
AUC_{0-12h}^{ss}	102.36 (29.30)	208.59 (59.28)	208.93 (57.30)
(ng · h/mL)			
C_{av}^{ss} (ng/mL)	8.53 (2.44)	17.38 (4.94)	17.41 (4.78)
C_{max}^{ss} (ng/mL)	12.67 (3.48)	25.67 (7.49)	30.50 (8.91)
C_{min}^{ss} (ng/mL)	4.06 (1.40)	8.98 (3.52)	8.78 (3.17)
DFL (%)	101.72 (14.14)	97.17 (18.80)	126.83 (27.93)
Swing	2.23 (0.64)	2.03 (0.70)	2.67 (0.92)
T_{max}^{ss} (h) ^a	2.00 (0.50-10.00)	2.00 (0.50-7.00)	6.50 (0.50-8.02)
$t_{1/2}$ (h) ^c	5.46 (1.24)	6.11 (1.46)	5.47 (1.70) ^b
K_{el} (1/h) ^c	0.1326 (0.0269)	0.1199 (0.0291)	0.1387 (0.0418) ^b

^aMedian (minimum-maximum).

^bN = 32

^cDays 5 to 7.

The PK behavior of APAP on Study Day 1 (see Table 41) was similar to that observed in the single dose study (see Example 10). Acetaminophen was rapidly absorbed following a single dose of 1 or 2 tablets of the ER formulation and in a similar fashion to the commercially-available immediate release tablet (FIG. 26). There was no lag in plasma concentrations following any of the 3 dosing regimens (median t_{lag} 0 hours), and no dose-dumping was observed for any subject. Peak APAP plasma concentrations were observed 30 to 45 minutes after administration of 1 or 2 tablets of the ER formulation and at 30 minutes after the first dose of the commercially-available immediate release tablet on Day 1. The C_{max} for APAP occurred following the first 325 mg dose of the commercially-available immediate release tablet, rather than after the second dose. Dose proportionality for C_{max} and AUC_{0-12h} was observed over the range of 325 mg to 650 mg APAP after a single administration of 1 or 2 tablets of the ER formulation. The C_{min} of APAP achieved steady-state levels by Day 4 for 1 tablet and by Day 2 for 2 tablets of the ER formulation and for the commercially-available immediate release tablet. Trough levels of APAP on Days 2 through 5 for 2 tablets of the ER formulation were comparable to those observed for the commercially-available immediate release tablet. On Day 1, interindividual variability (% CV) in C_{max} and AUC_{0-12h} for APAP was comparable between all 3 treatments (31% or less).

TABLE 41

APAP Pharmacokinetic Estimates - Day 1			
Parameter	Treatment A	Treatment B	Treatment C
	ER Formulation	ER Formulation	Commercially-available immediate release tablet
	(1 Tablet Q12 h)	(2 Tablets Q12 h)	(1 Tablet Q6 h)
	Mean (SD)	Mean (SD)	Mean (SD)
	(N = 33)	(N = 33)	(N = 33)
AUC_{0-12h}	12192 (3331)	24141 (6436)	24884 (6656)
(ng · h/mL)			
C_{max} (ng/mL)	2631 (815)	5245 (1473)	5146 (1553)
T_{max} (h) ^a	0.55 (0.25-3.00)	0.75 (0.25-2.00)	0.50 (0.25-8.00)
t_{lag} (h) ^a	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.00 (0.00-0.00)

^aMedian (minimum-maximum).

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Day 5 of the study, median T_{max}^{ss} for APAP was observed at 30 minutes following 1 or 2 tablets of the ER formulation and at 30 minutes following the first daily dose of the commercially-available immediate release tablet (see Table 42). Acetaminophen concentrations following administration of 325 mg or 650 mg APAP (1 or 2 tablets) Q12h were proportional to dose. The DFL in and swing of plasma APAP levels for the ER formulation were equivalent to the commercially-available immediate release tablet. On Day 5, interindividual variability (% CV) in C_{max}^{ss} for APAP was slightly higher following administration of 2 tablets of the ER formulation (33%) than the % CV seen for 1 tablet of the ER formulation and the commercially-available immediate release tablet (~27%). Interindividual variability in AUC_{0-12h}^{ss} for APAP was comparable between all 3 treatments (up to 27%).

TABLE 42

APAP Pharmacokinetic Estimates - Day 5

Parameter	Treatment A ER Formulation (1 Tablet Q12 h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12 h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6 h) Mean (SD) (N = 33)
AUC_{0-12h}^{ss} (ng · h/mL)	15307 (4092)	28512 (7714)	28719 (7023)
C_{av}^{ss} (ng/mL)	1276 (341)	2376 (643)	2393 (585)
C_{max}^{ss} (ng/mL)	3117 (840)	5872 (1932)	5968 (1639)
C_{min}^{ss} (ng/mL)	474.67 (163)	870.42 (336)	922.58 (321)
DFL (%)	212.08 (52.29)	218.06 (81.14)	213.79 (50.53)
Swing	5.95 (2.04)	6.63 (3.61)	5.94 (2.24)
T_{max}^{ss} (h) ^a	0.50 (0.25-3.00)	0.50 (0.25-3.02)	0.50 (0.25-8.02)
$t_{1/2}$ (h) ^c	5.60 (1.35) ^b	7.47 (2.89)	5.74 (2.98) ^b
K_{el} (1/h) ^c	0.1308 (0.0317) ^b	0.1026 (0.0292)	0.1416 (0.0515) ^b

^aMedian (minimum-maximum).^bN = 31^cDays 5 to 7.

Both OC and APAP were rapidly absorbed under all conditions with no lag in plasma concentrations. Both OC and APAP levels were sufficiently high within 1 hour after administration of the ER formulation as a single dose and at steady-state. OC levels were sustained over the proposed 12 h dosing interval. Plasma APAP concentrations decreased to below 1,000 ng/mL between doses of the ER formulation, thus minimizing the chances of its accumulation and the possibility of hepatotoxicity. Total exposure to both OC and APAP from the ER formulation was equivalent to that of the commercially-available immediate release tablet.

Example 12

Clinical Evaluation of the Safety and Analgesic Efficacy of an Extended Release Formulation of Oxycodone and Acetaminophen for Acute Pain

Pain relief for acute post-surgical pain requires immediate-release (IR) compounds acting within 1 hour of administration. These IR compounds, however, have a short half-life and require frequent administration; this is inconvenient to patients and leads to poor compliance. Such patients may benefit from an extended-release (ER) oral formulation of oxycodone hydrochloride (OC) and acetaminophen (APAP) that is designed to (1) provide the immediate-release of each drug to attain rapid therapeutic levels (within 1 hour of dosing) and (2) provide continuous release of each drug to main-

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tain the plasma levels of each drug within therapeutic windows for sustained analgesia (up to 12 hours). Furthermore, combining analgesics with distinct mechanisms of action provides maximum efficacy while reducing the toxicity of each agent, as the amount of OC and APAP can remain within the lower, safer end of their therapeutic windows. This ER formulation may provide the advantages of both immediate and prolonged pain relief from two analgesic compounds, potentially offering greater convenience to patients and greater dosing compliance. Accordingly, a study may be conducted to demonstrate the efficacy of repeated doses of 15 mg OC/650 mg APAP versus placebo, and to determine the safety and tolerability of multiple oral doses of the OC/APAP formulation administered to subjects with acute postoperative, moderate to severe pain.

The study will be conducted in the following phases: 1) pre-treatment phase consisting of a) screening, b) surgery, and c) recovery/qualification periods; 2) double-blind phase consisting of a single dose period followed by a multiple-dose period which begins with the request of the 2nd dose of study medication, and; 3) a voluntary open-label extension phase.

The single dose period of the double-blind phase will evaluate the onset and duration of analgesia of a single dose of 15 mg OC/650 mg APAP (as two 7.5/325 tablets) versus placebo. The time from the initial dose of study medication to the onset of perceptible pain relief and to the onset of meaningful pain relief will be measured. The subject will provide additional pain assessments (e.g., pain intensity will be measured using the 11 point NPRS scale at regular intervals).

The multiple dose period of the double-blind phase will evaluate the analgesic effects of multiple doses of 15 mg OC/650 mg APAP versus placebo with subjects dosed regularly every 12 hours for 48 hours. The multiple dose period will begin upon administration of the second dose after the subject's request for additional pain relief. Pain relief and intensity will be among the data measured in this arm of the study.

After completion of study evaluations 48 hours after the 2nd dose of study medication, subjects will be encouraged to enter the open-label extension phase of the study. During this time they will be provided with doses of 15 mg OC/650 mg APAP to be taken Q12h until no longer needed, for up to 14 days. The open-label extension phase (starting 48 hours after the second dose) will evaluate the safety profile as determined by adverse events (AE) and evaluate subject satisfaction with analgesic effects.

Example 13

Clinical Evaluation of the Safety and Efficacy of an Extended Release Formulation of Oxycodone and Acetaminophen for Chronic Pain

An open label safety study of doses of 15 mg OC/650 mg APAP administered at 12 hour intervals for up to 35 days in a patient population having pain associated with osteoarthritis (OA) of the knee or hip or chronic low back pain (CLBP) may be conducted. The primary objective of the study is to determine the safety and tolerability of doses of 15 mg OC/650 mg APAP for up to 35 days of use. Secondary objectives such as pain relief and changes in pain intensity will also be assessed.

Subjects enrolled in the study will be treated with 2 tablets of 7.5 mg OC/325 mg APAP every 12 hours (Q12h) for between 10 days and 35 days. Subjects will initially take 1 tablet of 7.5 mg OC/325 mg APAP under clinic supervision. Subjects will be observed for opioid tolerability symptoms. Subjects who experience opioid tolerability symptoms, or

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moderate to severe AEs, will be discontinued from the study. Subjects who do not experience opioid tolerability symptoms, or moderate to severe AEs, will be given a second tablet of 7.5 mg OC/325 mg APAP under clinic supervision. If subjects still do not experience opioid tolerability symptoms, or moderate to severe AEs, they will be sent home with supplies for dosing with 2 tablets of 7.5 mg OC/325 mg APAP Q12h for one week. If subjects do experience opioid tolerability symptoms, or moderate to severe AEs, they will be sent home with supplies for dosing with 1 tablet of 7.5 mg OC/325 mg APAP Q12h for one week.

Subjects that continue in the study beyond one week will continue to take 2 tablets Q12h for up to a total of 35 days, during which they will return to the clinic for subsequent assessments of safety and efficacy. After the Day 36 visit, subjects will be instructed to return to pre-study medication. Subjects whose pain subsides prior to the Day 36 visit, or who discontinue for other reasons will be instructed to return remaining study medication.

Example 14

Partial Areas Under the Curve for Oxycodone and Acetaminophen

Partial AUCs were calculated for a bilayer extended release tablet disclosed herein containing acetaminophen and oxycodone, and an immediate release acetaminophen and oxycodone tablet. Specifically, Partial AUCs were calculated for the acetaminophen and oxycodone tablets of (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10. These results are summarized in Tables 43-46.

TABLE 43

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.			
Study	AUC _{0-1.7h} (ng · h/mL)	AUC _{1.7-48h} (ng · h/mL)	AUC _{0-∞} (ng · h/mL)
Treatment B (Ex. 10)	6029	28435	32644
Treatment C (Ex. 9)	5854	25539	29741

TABLE 44

Additional Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.					
Study	AUC _{0-12h} (ng · h/mL)	AUC _{1-12h} (ng · h/mL)	AUC _{12-36h} (ng · h/mL)	AUC _{8-12h} (ng · h/mL)	AUC _{0-∞} (ng · h/mL)
Treatment B (Ex. 10)	25912	22615	7978	4401	32644
Treatment C (Ex. 9)	24102	20875	6854	3910	29741

TABLE 45

Percent of AUC _{0-∞} for Acetaminophen				
Study	AUC _{0-12h} (dosing interval)	AUC _{1-12h} (T _{max} to end of dosing interval)	AUC _{12-36h} (end of dosing interval to last concentration)	AUC _{8-12h}
Treatment B (Ex. 10)	79%	69%	24%	13%
Treatment C (Ex. 9)	81%	70%	23%	13%

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TABLE 46

Mean(SD) Parameter Estimates for Partial AUCs for Oxycodone.			
Study	AUC _{0-2.8h} (ng · h/mL)	AUC _{2.8-48h} (ng · h/mL)	AUC _{0-∞} (ng · h/mL)
Treatment B (Ex. 10)	28.75	158.49	185.93
Treatment C (Ex. 9)	27.89	164.27	190.66

The bioequivalence determinations between two tablets of a pharmaceutical composition described herein, each containing 7.5 mg oxycodone and 325 mg acetaminophen and an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen can be found in Tables 47 and 48.

TABLE 47

Bioequivalence Determination for Acetaminophen			
Parameter	LSM Ratio	90% CI	
		Lower	Upper
Ln(AUC _{0-1.7h})	101.97	82.90	125.43
Ln(AUC _{1.7-48h})	91.15	80.58	103.11
Ln(AUC _{0-∞})	93.14	82.40	105.28

TABLE 48

Bioequivalence Determination for Oxycodone			
Parameter	LSM Ratio	90% CI	
		Lower	Upper
Ln(AUC _{0-2.8h})	99.04	87.83	111.68
Ln(AUC _{2.8-48h})	103.21	92.57	115.06
Ln(AUC _{0-∞})	102.19	92.34	113.09

The results demonstrate that the plasma concentrations of both oxycodone and acetaminophen rose rapidly with no lag time for a pharmaceutical composition of the present invention and an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen. See FIG. 29. Further, 30 minutes after administration of a dose of a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen), oxycodone levels were within the therapeutic range (>5 ng/mL). Thus, an analgesic effect will be seen in opioid naïve patients. In addition, a pharmaceutical composition of the present invention was able to maintain oxycodone levels above 5 ng/mL for up to 12 hours after dosing, suggesting that the analgesic effect may extend to the next dosing cycle.

Concentrations of acetaminophen resulting from a dose of a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen), decreased to less than 900 ng/mL (>17% of C_{max}) by 12 hours after administration. This decreased concentration of acetaminophen at the end of the dosing cycle allows for sufficient acetaminophen or "APAP time off" between doses.

Oxycodone and acetaminophen levels from a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen) declined at a similar rate to an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen, with a terminal elimination half-life of approximately 4 to 5 hours.

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Example 15

Partial Areas Under the Curve for Oxycodone and Acetaminophen Administered with Food

Partial AUCs were calculated for a bilayer extended release tablet disclosed herein containing acetaminophen and oxycodone, and an immediate release acetaminophen and oxycodone tablet. Specifically, Partial AUCs were calculated for the acetaminophen and oxycodone tablets of (1) Treatment A of Example 4, (2) Treatment A of Example 6 (one tablet), and (3) Treatment C of Example 4. These results are summarized in Tables 49-50.

TABLE 49

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.			
Study	AUC _{0-3.2h} (ng · h/mL)	AUC _{3.2-48h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment A (Ex. 4)	8042	23810	30245
Treatment A (Ex. 6) (one tablet)	9145	23319	31478

TABLE 50

Mean (SD) Parameter Estimates for Partial AUCs for Oxycodone.			
Study	AUC _{0-4.3h} (ng · h/mL)	AUC _{4.3-48h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment A (Ex. 4)	48.62 (15.99)	152.57 (49.86)	199.43 (59.47)
Treatment A (Ex. 6) (one tablet)	53.29 (17.12)	167.50 (51.83)	219.20 (55.99)

The bioequivalence determinations between the pharmaceutical composition described herein, containing 15 mg oxycodone and 650 mg acetaminophen and an immediate release product comprising 15 mg oxycodone and 650 mg acetaminophen can be found in Tables 51 and 52.

TABLE 51

Bioequivalence Determination for Acetaminophen			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-3.2h})	114.46	96.21	136.16
Ln(AUC _{3.2-48h})	94.62	83.31	107.47
Ln(AUC _{0-t})	101.32	90.00	114.07

TABLE 52

Bioequivalence Determination for Oxycodone			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-4.3h})	109.87	94.98	127.08
Ln(AUC _{4.3-48h})	109.75	94.48	127.48
Ln(AUC _{0-t})	110.53	97.39	125.44

Exposure to oxycodone and acetaminophen was comparable between Treatment A of Example 4 and Treatment A of Example 6 (one tablet). Thus, these results indicate that the

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release of oxycodone and acetaminophen is consistent across studies. Plasma concentration-time profiles are presented in FIGS. 30A and 30B.

The initial exposure to oxycodone (AUC_{0-4.3h}) was slightly outside the bioequivalence parameters established by the FDA (upper 90% CI 127%). The initial exposure to acetaminophen (AUC_{0-3.2h}) was outside of the FDA's bioequivalence parameters (upper 90% CI 136%).

The extended (sustained) exposure to oxycodone (AUC_{4.3-48h}) was slightly outside the FDA's limit for bioequivalence (upper 90% CI 127%). However, the extended exposure to acetaminophen (AUC_{3.2-48h}) and total exposure (AUC_{0-t}) for both oxycodone and acetaminophen was equivalent between studies.

Example 16

Mechanical Crushing into Powder Form

Drug abusers often tamper with extended release opioid-containing formulations by crushing the dosage form. This process generally serves several functions, including destroying the extended release properties of the dosage form and enabling the dosage form to be processed for unintended methods of administration, such as snorting or intravenous injection. Accordingly, comparative tamper resistance experiments were performed on a tablet dosage form of the pharmaceutical composition of the present invention containing 7.5 mg oxycodone HCl and 325 mg acetaminophen (see Chart 1) (the "product") and a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the "comparator").

The product and comparator tablets were subjected to standard mechanical crushing by the following means: a hammer, a pill crusher, a mortar and pestle, a knife, two spoons, a utility knife, a blender, a coffee mill, and a coffee grinder. The success or failure of the particle size reduction was then visually assessed. In some cases, a sieving analysis was also utilized to quantitatively measure if significant particle size reduction occurred. Generally, drug abusers desire to crush pharmaceutical formulations into a fine powder, as this form is convenient for processing the tablet into a snortable or injectable form.

The results demonstrated that in most instances, the comparator was easily broken down into smaller pieces by each of the mechanical means listed above. Accordingly, in most instances, the comparator offered little tamper resistance as it could easily be mechanically crushed into a suitable powder. In contrast, the physical properties of the product tablet prevented the product tablet from being crushed into a fine powder. Indeed, in relation to the comparator, the product tablet was more difficult to break down using the methods listed above. Specifically, all of the mechanical methods described above were ineffective at producing a suitable powder from the product tablets except grinding in a mortar and pestle. Consequently, the product tablets offer improved protection from the mechanical crushing methods employed by drug abusers.

Example 17

Abuse Resistance Properties of Product Powders Produced by Grinding Using a Mortar and Pestle

An in vitro dissolution test with human abuse liability ("HAL") predictions was conducted to determine the cumulative amount of drug released from intact and crushed tablets

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of the pharmaceutical compositions disclosed herein and a commercially-available immediate release oxycodone and acetaminophen tablet.

Comparator tablets (the “comparator”) containing a total of 7.5 mg of oxycodone HCl and a total of 325 mg acetaminophen were obtained. Six comparator tablets were ground with a mortar and pestle and placed into capsules, while six tablets were used as is (i.e., kept intact, but placed into capsules). Dissolution profiles for the intact and crushed tablets were determined in a USP type II apparatus. Six intact tablets and six crushed tablets were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. ±0.5° C. The mixture was stirred at 100 ± 4 rpm, and the temperature was maintained at 37° C. ±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 5 min, 10 min, 20 min, 30 min, and 60 min. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures. The release profile of oxycodone HCl from intact and crushed comparator is shown in FIG. 31.

Bilayer formulations described herein were prepared, each containing a total of 7.5 mg of oxycodone HCl, a total of 325 mg of acetaminophen, and an extended release polymer. Six product tablets (as defined in Example 16) were ground with a mortar and pestle and placed into capsules, while twelve product tablets were used as is. The same dissolution method as described for the intact and crushed comparator above was used to obtain release profiles for intact and crushed product tablets. However, six of the intact product tablets (labeled as “Intact”) were sampled (5 mL) at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The release profiles of acetaminophen and oxycodone HCl from the intact and crushed product tablets are shown in FIGS. 32 and 33, respectively. In these figures, “intact” refers to the intact product tablets sampled at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. “HAL_Intact” refers to the intact product tablets sampled at the same time intervals as the crushed tablets, namely, 5 min, 10 min, 20 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr.

These results show that for release of oxycodone HCl from the comparator tablets, there is no substantial difference in the release profiles for crushed and intact tablets for abuse purposes. In each case, almost all of the oxycodone HCl was released in as little as ten minutes. In stark contrast, there are substantial differences in the release profiles for crushed and intact product tablets. The intact product tablets surprisingly exhibited a higher release rate of both active ingredients than the crushed product tablets in the first hour. This suggests that upon grinding the product tablets, the active ingredients in the immediate release portion are incorporated into the extended release portion, and the product tablet loses its immediate release characteristics. This feature may effectively negate a drug abuser’s purpose for crushing the product tablet in the first place—to obtain an early onset of analgesia.

Predicted pharmacokinetic parameters were obtained for these in vitro release profiles for the crushed and intact products and comparator tablets by using in vitro in vivo correlation (“IVIVC”) technique. These results, which are summarized in Table 53, demonstrate that the abuse quotients for the crushed and intact comparator tablets are orders of magnitude higher than the abuse quotients for the crushed and intact product tablets. This is consistent with the experimentally determined pharmacokinetic parameters from Example 10.

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TABLE 53

Predicted pharmacokinetic parameters and abuse quotient for intact and crushed product and comparator tablets.			
Product	C _{max} (ng/mL)	T _{max} (hr)	Abuse Quotient (ng/mL · hr)
Predicted			
Comparator (intact)	32.5	0.16	203.1
Comparator (crushed)	30.8	0.17	181.2
Product (intact)	17.5	6	2.9
Product (crushed)	20.6	4	5.2
Experimental - see Example 10			
Comparator (intact)	41.6	0.7	59.4
Product (intact)	16.4	3.2	5.1

Example 18

Preconditioning the Tablets by Crisping

Drug abusers often precondition the tablet by a process known as crisping. This procedure is intended to remove some of the tablet fillers, making the drug easier to crush and insufflate or inject. Accordingly, an experiment was performed to determine a drug abuser’s ability to crisp a tablet dosage form of the pharmaceutical composition of the present invention containing 7.5 mg oxycodone HCl and 325 mg acetaminophen (see Chart 1) (the “product”) as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the “comparator”).

First, the product and comparator tablet were crushed into a powder and placed in a spoon. The spoon was then heated from underneath with an open flame. Once the powder began to caramelize and smoke, the heat was removed and the powder was mixed using a metal spatula. The spoon was again heated until the powder began to caramelize further. The heat was once again removed, and the powder was allowed to cool. The resulting powders were then removed from the spoon and placed in a mortar and pestle for subsequent crushing. The comparator tablet resulted in a powder that could be easily crushed into a fine powder. Unlike the comparator tablet, the product tablet resulted in a sticky composition, rendering the product tablet unsuitable for grinding into a fine powder after the crisping process.

Example 19

Separation Studies

To determine the ease at which the immediate release (IR) and extended release (ER) layers of a bilayer form of the pharmaceutical composition disclosed herein could be tampered with, several attempts were made at separating the immediate release (IR) and extended release (ER) layers of the product (as defined in Example 18). Initially, a tablet dosage form of the pharmaceutical composition of the present invention was positioned with the inscribed side facing up and cut completely through vertically. Upon slicing the tablet, observations revealed no visual distinction between the IR and ER layers. The tablet was then re-oriented and sliced from several additional angles. However, no demarcation line was observed between the IR and ER layers. Consequently, a drug abuser could not visually distinguish the IR and ER layers of the pharmaceutical composition disclosed herein by simply cutting the dosage form.

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Example 20

Injectability Studies

An injectability study was conducted to determine the extent to which crushed and dissolved tablets of the pharmaceutical composition disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (the “product”) could be drawn into a syringe for intravenous administration as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen that had been crushed and dissolved (the “comparator”). Intravenous administration is a common practice used by drug abusers as a means to potentiate their drugs by administering the drug as one large bolus instead of a steady release over time. Two measureable entities were evaluated: the amount of useable fluid that was harvested through the process and the concentration of oxycodone in these aliquots. This study employed a standard 1 mL insulin syringe equipped with 22-, 26-, and 30-gauge needles, which are the typical sizes of needles used by intravenous drug users.

An intact product and comparator tablet were each ground in a mortar and pestle to yield a fine powder. The powder was then placed onto a tablespoon secured to a laboratory ring stand. 3 mL of deionized water was added to the spoon and was mixed into a slurry in an attempt to dissolve the active ingredient. To enhance solubility of the drug, a butane lighter was used to uniformly heat the bottom of the spoon. When the solution began to boil slightly, heat was removed and any liquid lost was replenished. A traditional insulin syringe (1 mL) with a makeshift cotton ball filter and the various gauge needles was used to extract the resulting liquid into the syringe.

Three types of cotton filters were evaluated for use in this procedure. The first filter was a small cotton plug placed between the needle hub and barrel of the syringe. This filter clogged for all three gauges when attempts were made to draw liquid into the syringe. The second filter was formed by inserting the tip of the syringe needle into the end of a Q-tip. This second filter also prevented an appreciable amount of fluid to be drawn into the syringe. The third filter was a small piece of cotton attached to the end of the needle. The third filter was chosen for further study because it was the only filter evaluated in which liquid could be drawn into the syringe for all three gauges without clogging the filter. The drawn liquid was collected, measured and quantified by LC/MS/MS analysis.

When water was mixed with the ground product tablet, the solid did not completely dissolve upon heating. Instead, a pasty material was produced that did not readily disperse when mixed. The product required almost constant mixing of the crushed powder and water with constant heating to produce a removable liquid. It was difficult to generate a homogeneous mixture of liquid that could be drawn into a syringe because the combined volume of the crushed product tablet and the 3 mL of water essentially filled the spoon to capacity. Additionally, with heating, it was necessary to replenish the evaporated water to maintain a constant slurry level in the spoon. Liquid samples were drawn from the bottom of the spoon with a 1 mL syringe with the cotton plug on the tip. This study demonstrated that only about 1 mL of liquid could consistently be drawn into the syringe, independent of needle size. The resulting liquid in the syringe was murky and not transparent due to particulate matter.

In contrast, a large portion of the comparator readily dissolved when mixed and heated in the tablespoon. The result-

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ing liquid in the syringe therefore contained much less particulate matter than the liquid resulting from the product tablet.

These results indicate that injection is not a preferred form of drug diversion for the product tablets. When adding water to the ground tablets, the user may recover only a small portion of that liquid for use in a syringe. The product tablet tended to produce a semi-solid paste that interfered with liquid recovery through the syringe. The overall results indicate a recovery of less than 20% of the oxycodone in the product tablet.

Example 21

Snorting Studies

Another method of tampering and diversion is to grind a tablet into a fine powder and insufflate (snort) the powder. The inhaled powder is deposited inside the nasal passage, and the oxycodone is absorbed through the mucous membranes of the nasal passage. In order for the procedure to work efficiently, the powder must deposit as a thin layer onto the nasal tissue in the sinus cavity. A study was performed to estimate the effectiveness of this process using the pharmaceutical composition disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (the “product”) and a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the “comparator”).

Product tablet and a comparator tablet were ground in a mortar and pestle. 1 mL of water was added to each ground tablet, and the resulting combination was mixed in an attempt to produce a thin slurry, which mimics the interface between the nasal passage and the absorptive tissue. The product tablet formed a paste that tended to clump. The comparator produced a more fluid consistency. Consequently, the comparator produced a more effective coating for absorption of insufflated oxycodone in the nasal cavity than the product disclosed herein.

Example 22

Dose Dumping Studies

Dose dumping is the process of releasing the active ingredient(s) of an extended release pharmaceutical formulation in a short period of time in a manner in which the entire dosage, or a significant portion of the dosage, becomes available for absorption in the body. This is often achieved by ingesting tablets along with alcoholic beverages to enhance drug delivery. The alcohol serves as a means to act on either the coating of a tablet to help release the active ingredients or to promote greater absorption within the body. This method is employed by drug abusers as an attempt to potentiate analgesic drugs. Release of elevated quantities of drug can lead to increased euphoric effects but can also cause adverse effects, some of which may be fatal.

Two dissolution experiments were performed in a dose dumping study. The dissolutions were designed to examine the differences between intact pharmaceutical compositions disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (the “product”) and a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the “comparator”) when exposed to simulated gastric fluid dissolution media (“SGF”). The first dissolution was performed in 75 mL of SGF in the absence of vodka. The second dissolution was performed in 75 mL of a 50:50 mixture of SGF and 80-proof vodka. This was designed

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to measure the extent that the product and comparator may be abused by the simultaneous intake of alcohol. Both dissolutions were performed at room temperature and were mixed on a stir plate. Aliquots were removed at 0.25, 0.50, 1, 2 and 4 hours for quantification by LC/MS/MS, a summary of which is contained in Table 54 below.

TABLE 54

Mean percent recovery of oxycodone in (i) simulated gastrointestinal fluid and (ii) a solution containing 50% simulated gastric fluid and 50% 80-proof vodka.						
Mean Percent Recovery at time = t						
Fluid	Intact Tablet	0.25 hr	0.5 hr	1 hr	2 hr	4 hr
SGF	Product	15%	30%	43%	57%	80%
SGF	Comparator	104%	102%	105%	102%	100%
SGF:EtOH	Product	12%	23%	35%	46%	62%
SGF:EtOH	Comparator	101%	101%	103%	100%	102%

At the end of the four hour dissolution, the product tablets were still visible but had lost their outer coating in SGF both in the presence and absence of vodka. Addition of ethanol to the SGF produced a slight decrease in the dissolution rate of the product tablet. Comparator tablets were dissolved in SGF both in the presence and absence of vodka after five minutes. Consequently, the product tablets were resistant to dose dumping when compared to the comparator tablets.

Example 23

Clinical Evaluation of the Relative Abuse Potential of an Extended Release Formulation of Oxycodone and Acetaminophen

A study may be performed to assess the relative abuse potential of a bilayer, extended-release oral formulation disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (see Chart One) versus an immediate release oxycodone HCl/acetaminophen tablet in non-dependent, recreational opioid users. The study will consist of a screening period, and in-clinic period, and a follow-up period.

The study will consist of seven treatment periods, each of which will involve a single treatment of one of the study medications followed by a wash-out period. Tests will be conducted to ensure that the subjects are not physically dependent on opioids, and that they can discriminate between the effects oxycodone versus the placebo. Upon completion, the study medications will be randomly administered as a single oral dose to each subject and consist of the following:

Group A: two tablets disclosed herein containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus two placebo tablets disclosed herein plus four placebo immediate release capsules.

Group B: four tablets disclosed herein containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus four placebo immediate release capsules.

Group C: two immediate release capsules containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus two placebo immediate release capsules plus four placebo tablets disclosed herein.

Group D: four immediate release capsules containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus four placebo tablets disclosed herein.

Group E: two crushed tablets disclosed herein containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each placed in four capsules plus four placebo tablets disclosed herein.

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Group F: two crushed immediate release tablets containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each placed in two capsules plus two placebo immediate release capsules.

Group G: four placebo tablets disclosed herein plus four placebo immediate release capsules.

Subjects will receive seven treatments according to their treatment sequence, and doses will be separated.

Example 24

Varying Polyox Grades Comprising 25% by Weight of the Extended Release Portion of Bilayer Formulations

Single layer tablet formulations containing only the extended release portion were prepared, each tablet containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for the bilayer tablet and 60% of the total oxycodone HCl for the bilayer tablet. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 25% by weight of the ER portion, and therefore, the tablet weight. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the tablet of ER portion. In a third formulation, POLYOX® N-60K was employed as the extended release component in an amount of 25% by weight of the tablet or ER portion.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. ± 0.5° C. The mixture was stirred at 150 ± 6 rpm, and the temperature was maintained at 37° C. ± 0.5° C. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the Polyox 205 was 17 hrs; the final time point for the Polyox 1105 was 15 hrs; and the final time point for the Polyox N60k was 18 hrs and 40 minutes. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 34 and 35, respectively. This data represents dissolution for the extended release portion with the immediate release data theoretically added. These figures demonstrate that as the average molecular weight of the POLYOX® extended release component increases, the rate of dissolution at each time point decreases. For example, the formulations containing

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POLYOX® 205, 1105, and N-60K had released about 59%, about 56%, and about 55% acetaminophen after 15 minutes, respectively; about 63%, about 59%, and about 57% acetaminophen after 30 minutes, respectively; about 69%, about 64%, and about 61% acetaminophen after 1 hr, respectively; about 78%, about 73%, and about 67% acetaminophen after 2 hr, respectively; about 91%, about 87%, and about 76% acetaminophen after 4 hr, respectively; about 97%, about 95%, and about 84% acetaminophen after 6 hr, respectively; and about 98%, about 97%, and about 90% acetaminophen after 8 hr, respectively.

The same general trend of a decreased release rate with a higher molecular weight POLYOX® grade was also observed for the oxycodone. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 53%, about 50%, and about 48% oxycodone after 15 minutes, respectively; about 60%, about 56%, and about 53% oxycodone after 30 minutes, respectively; about 68%, about 63%, and about 59% oxycodone after 1 hr, respectively; about 80%, about 75%, and about 67% oxycodone after 2 hr, respectively; about 94%, about 91%, and about 80% oxycodone after 4 hr, respectively; about 100%, about 98%, and about 89% oxycodone after 6 hr, respectively; and about 100%, about 99%, and about 95% oxycodone after 8 hr, respectively.

Example 25

Varying Polyox Grades Comprising 45% by Weight of the Extended Release Portion of Bilayer Formulations

Single layer formulations containing only the extended release portion described herein were prepared, each tablet containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for a bilayer tablet and 60% of the total oxycodone HCl for a bilayer tablet. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a third formulation, POLYOX® N-60K was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. The other excipients in the extended release portion were microcrystalline cellulose, sprss B825, citric acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate.

Dissolution profiles for the three above-described formulations were Determined in USP Type II apparatus. Six tablets of each formulation were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6, hr, 8 hr, and 12 hr. The final time point for the Polyox 205 was 17 hours; the final time point for Polyox 1105 was 17.5 hours; and the final time point for Polyox N60k was 23.5 hours. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 36 and 37, respectively. This data represents dissolution for the extended release portion with the immediate release data

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theoretically added. Consistent with the results of Example 24, the rate of dissolution at each time point decreases as the molecular weight of POLYOX® increases. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 53%, about 53%, and about 53% acetaminophen after 15 minutes, respectively; about 56%, about 55%, and about 54% acetaminophen after 30 minutes, respectively; about 61%, about 60%, and about 57% acetaminophen after 1 hr, respectively; about 70%, about 67%, and about 63% acetaminophen after 2 hr, respectively; about 81%, about 71% acetaminophen after 4 hr, respectively; about 95%, about 90%, and about 79% acetaminophen after 6 hr, respectively; about 99%, about 95%, and about 85% acetaminophen after 8 hr, respectively; and about 99%, about 96% and about 93% acetaminophen after 12 hr.

The formulations containing POLYOX® 205, 1105, and N-60K also released about 47%, about 47%, and about 46% oxycodone after 15 minutes, respectively; about 51%, about 50%, and about 49% after 30 minutes, respectively; about 59%, about 56%, and about 53% oxycodone after 1 hr, respectively; about 70%, about 67%, and about 62% oxycodone after 2 hr, respectively; about 88%, about 83%, and about 74% oxycodone after 4 hr, respectively; about 99%, about 93%, and about 83% oxycodone after 6 hr, respectively; and about 100%, about 97%, and about 90% oxycodone after 8 hr, respectively.

Example 26

Varying the Concentrations of a Specific Polyox Grade in the Extended Release Portion of Bilayer Formulations

The data from Examples 24 and 25 indicate that an increase in the amount of POLYOX® in the pharmaceutical composition retards the release of oxycodone and acetaminophen from the pharmaceutical composition. To confirm this observation, single layer extended release formulations described herein were prepared, each containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for the bilayer tablet and 60% of the total oxycodone for the bilayer tablet. In a first formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the tablet or ER portion. In a second formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 35% by weight of the tablet or ER portion. In a third formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a fourth formulation, POLYOX® 1105 was employed as the extended release component in an amount of 55% by weight of the tablet or ER portion. The amount of the microcrystalline cellulose in the four formulations was adjusted to account for the differing amounts of POLYOX® 1105 in each formulation. The other excipients in the extended release portion were B825, citric acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate. However, the percentages for all the other excipients remained the same for each formulation, and were consistent with the percentages used in Example 25.

Dissolution profiles for the above-described formulations were determined in USP Type II apparatus. Six tablets of each formulation were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C.

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The mixture was stirred at 150 ± 6 rpm, and the temperature was maintained at $37^\circ \text{C} \pm 0.5^\circ \text{C}$. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the 25%, 35%, 45%, and 55% formulations was 15 hr, 15 hr, 17.5 hr, and 17.5 hr, respectively. Each sample was filtered through a $0.45 \mu\text{m}$ filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 38 and 39, respectively. These profiles confirm that as the amount of POLYOX® 1105 used in the pharmaceutical formulations increase, the release rate of the acetaminophen and oxycodone generally decreases. For example, the formulations containing 25%, 45%, and 55% POLYOX® 1105 had released about 56%, about 53%, and about 53% acetaminophen after 15 minutes, respectively; about 59%, about 56%, about 55%, and about 55% acetaminophen after 30 minutes, respectively; about 64%, about 61%, about 60%, and about 59% acetaminophen after 1 hr, respectively; about 73%, about 70%, about 67%, and about 66% acetaminophen after 2 hr, respectively; about 87%, about 84%, about 81%, and about 79% acetaminophen after 4 hr, respectively; about 95%, about 93%, about 90%, and about 89% acetaminophen after 6 hr, respectively; about 97%, about 97%, about 95%, and about 95% acetaminophen after 8 hr, respectively; and about 97%, about 97%, about 96%, and about 98% acetaminophen after 12 hr, respectively.

Similar trends were observed for the cumulative release of oxycodone. However, there was no observable difference in the release of oxycodone from the formulations containing 45% and 55% POLYOX® 1105. For example, the formulations containing 25%, 45%, and 55% POLYOX® 1105 had released about 50%, about 47%, and about 45% oxycodone after 15 minutes, respectively; about 56%, about 51%, about 50%, and about 50% oxycodone after 30 minutes, respectively; about 63%, about 58%, about 56%, and about 56% oxycodone after 1 hr, respectively; about 75%, about 70%,

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about 67%, and about 66% oxycodone after 2 hr, respectively; about 91%, about 87%, about 83%, and about 82% oxycodone after 4 hr, respectively; about 98%, about 96%, about 93%, and about 93% oxycodone after 6 hr, respectively; about 99%, about 99%, about 97%, and about 98% oxycodone after 8 hr, respectively; and about 99%, about 100%, about 97%, and about 100% oxycodone after 12 hr, respectively.

Example 27

In Vitro Dissolution of Controlled-Release Bilayer Tablets Containing 7.5 mg Oxycodone and 325 mg Acetaminophen Performed at a 100 rpm Paddle Speed

Three batches of bilayer formulations described herein were prepared, each containing a total of 7.5 mg of oxycodone HCl and a total of 325 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the oxycodone HCl was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations of each batch were determined in a USP Type II apparatus. Twelve tablets from each batch were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to $37^\circ \text{C} \pm 0.5^\circ \text{C}$. The mixture was stirred at 100 ± 4 rpm, and the temperature was maintained at $37^\circ \text{C} \pm 0.5^\circ \text{C}$. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a $0.45 \mu\text{m}$ filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and oxycodone from each batch are described in Table 55.

TABLE 55

Release rate data of bilayer tablets (7.5 mg oxycodone HCl; 325 mg acetaminophen) using a 100 rpm dissolution method.								
Time	Oxycodone HCl				Acetaminophen			
(Hours)	Mean (%)	RSD	Min (%)	Max (%)	Mean (%)	RSD	Min (%)	Max (%)
Batch 1								
0.25	31.7	2.1	30.6	32.5	51.8	1.4	50.9	53.1
0.5	37.1	1.3	36.3	37.8	54.3	1.3	53.5	55.6
1.0	45.4	1.0	44.9	46.0	58.6	1.2	57.7	60.1
2.0	58.5	1.3	57.4	59.7	66.0	1.2	64.8	67.7
4.0	78.6	1.7	76.8	80.5	78.5	1.5	77.0	80.6
6.0	92.2	1.8	90.0	94.7	88.0	1.6	86.0	90.3
8.0	99.5	1.8	97.4	102.7	93.8	1.5	91.8	96.3
12.0	101.7	1.4	99.7	104.3	96.1	1.0	94.9	98.2
Batch 2								
0.25	31.6	3.5	29.6	34.0	52.1	4.0	48.8	55.8
0.5	37.2	3.2	34.9	39.9	54.5	3.8	51.4	58.3
1.0	45.4	3.3	42.4	48.3	59.1	3.5	56.0	63.1
2.0	58.9	1.7	57.3	61.1	66.4	3.0	63.6	70.0
4.0	79.1	1.5	77.7	81.5	78.7	2.5	75.4	81.8
6.0	93.1	1.3	91.5	95.8	87.7	2.2	84.4	90.7
8.0	100.2	1.2	98.7	102.3	93.5	1.9	90.4	96.2
12.0	102.7	1.3	100.4	104.4	95.6	2.0	92.6	98.4

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TABLE 55-continued

Release rate data of bilayer tablets (7.5 mg oxycodone HCl; 325 mg acetaminophen) using a 100 rpm dissolution method.								
Time	Oxycodone HCl				Acetaminophen			
(Hours)	Mean (%)	RSD	Min (%)	Max (%)	Mean (%)	RSD	Min (%)	Max (%)
Batch 3								
0.25	30.4	1.6	29.3	31.0	52.2	2.3	49.6	54.2
0.5	35.7	1.6	34.2	36.7	54.6	2.3	52.0	56.6
1.0	43.5	1.8	42.0	45.1	58.6	2.2	56.0	60.8
2.0	56.1	1.9	54.4	58.0	65.5	2.1	63.1	68.0
4.0	75.4	1.8	73.3	77.6	77.3	2.0	74.8	80.0
6.0	88.9	1.7	86.1	91.4	86.5	2.2	83.7	90.1
8.0	97.0	1.5	94.7	99.8	93.0	2.1	90.1	96.8
12.0	100.4	1.1	98.7	102.4	96.5	1.6	93.2	98.3

Example 28

In Vitro Dissolution of Controlled-Release Bilayer
Tablets Containing 15 mg Oxycodone and 650 mg
Acetaminophen Performed at a 150 rpm Paddle
Speed

Bilayer formulations described herein were prepared, each containing a total of 15 mg of oxycodone HCl and a total of 650 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the oxycodone HCl was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations were determined in a USP Type II apparatus. Six tablets were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.55° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and oxycodone from each batch are described in Table 56.

TABLE 56

Release rate data of bilayer tablets (15 mg oxycodone HCl; 325 mg acetaminophen) using a 150 rpm dissolution method.		
Time (hr)	Oxycodone HCl (%)	Acetaminophen (%)
0.25	33.7	54.4
0.50	39.0	56.5
1	47.4	60.6
2	61.4	68.1
4	81.7	81.1
6	95.2	90.8
8	101.2	96.0
12	102.3	97.6

Example 29

Ethanol Release Testing at a 100 rpm Paddle Speed

The ethanol release studies discussed above in Example 8 were repeated, except that the solutions were stirred at a

paddle speed of 100 rpm and additional aliquots were sampled at 240 min and 480 min. Tables 57, 58, 59, 60, and 61 present the percent release of OC and APAP in the presence of 0%, 5%, 10%, 20%, and 40% ethanol, respectively. FIG. 40 presents dissolution profiles for OC and FIG. 41 presents dissolution profiles for APAP in the presence of 0%, 5%, 20%, and 40% ethanol. Like the results at a paddle speed of 150 rpm, these data reveal that, for both OC and APAP, the dissolution in 5%, 20%, or 40% ethanol was either comparable or slower than the dissolution in 0% ethanol, indicating no dose dumping for this formulation.

TABLE 57

Percent Release in 0% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	32.5	3.7	31.5	36.0	52.2	1.6	50.7	53.4
30	37.6	2.5	36.6	39.9	54.6	1.4	53.2	55.7
45	42.1	2.7	40.9	44.8	56.8	1.4	55.3	57.9
60	45.8	2.1	44.6	48.1	58.8	1.4	57.4	59.8
75	49.6	2.3	48.2	52.2	60.8	1.4	59.2	61.8
90	53.1	2.4	51.7	55.8	62.6	1.4	60.9	63.8
105	56.3	2.4	54.8	59.3	64.3	1.4	62.6	65.6
120	59.5	2.5	57.6	63.0	66.0	1.4	64.2	67.3
240	80.3	2.5	77.3	84.9	78.6	1.8	76.3	80.6
480	102.4	1.8	100.5	107.2	95.5	1.6	92.6	97.7

TABLE 58

Percent Release in 5% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	31.5	2.5	30.0	32.9	52.6	2.1	51.4	55.1
30	36.8	2.4	35.6	38.5	55.1	2.0	53.8	57.6
45	40.9	2.8	38.9	43.5	57.1	2.0	55.8	59.6
60	44.6	3.7	42.1	48.4	58.9	2.0	57.6	61.4
75	48.0	3.6	46.0	52.6	60.7	1.9	59.4	63.2
90	51.0	3.1	49.3	55.3	62.3	1.9	61.0	64.7
105	54.3	3.2	51.8	58.6	63.9	2.0	62.6	66.4
120	57.1	3.2	54.6	61.7	65.5	1.9	64.1	67.8
240	76.6	3.2	73.8	83.0	77.2	2.1	75.5	80.6
480	99.9	2.7	95.8	106.8	94.4	1.7	92.6	98.1

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TABLE 59

Percent Release in 10% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	30.3	3.1	28.9	32.1	51.7	1.8	50.1	53.4
30	35.6	3.3	33.7	37.3	54.1	1.9	52.4	55.8
45	39.6	2.6	37.6	40.9	56.0	1.9	54.3	57.8
60	43.1	2.6	41.2	44.7	57.8	1.9	56.1	59.5
75	46.2	2.3	44.1	47.5	59.5	1.8	57.7	61.1
90	49.3	2.1	47.3	50.6	61.1	1.8	59.3	62.8
105	52.2	2.2	50.1	53.6	62.6	1.8	60.9	64.2
120	54.8	2.3	52.8	56.4	64.1	1.8	62.3	65.6
240	73.8	2.2	70.8	76.1	75.5	1.7	73.4	77.4
480	98.4	2.1	94.7	101.1	93.5	1.6	91.0	95.9

TABLE 60

Percent Release in 20% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	28.0	6.0	23.9	30.3	50.2	5.1	43.0	53.0
30	33.6	4.5	30.7	35.6	53.4	3.1	49.5	55.9
45	37.9	2.9	35.7	39.6	55.5	2.6	52.6	57.9
60	41.2	3.1	39.2	43.2	57.3	2.3	55.1	59.8
75	44.1	2.9	42.3	46.6	59.0	2.2	57.0	61.4
90	46.5	3.5	42.7	49.1	60.5	2.1	58.6	62.9
105	49.8	2.9	48.0	52.8	61.9	2.1	60.2	64.4
120	52.2	2.8	49.9	54.8	63.3	2.0	61.7	65.9
240	72.2	2.1	69.4	74.7	76.0	1.7	74.1	78.4
480	95.7	2.3	91.7	98.7	91.9	1.7	89.3	94.6

TABLE 61

Percent Release in 40% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Min-imum	Max-imum	Mean	RSD	Min-imum	Max-imum
15	11.9	13.9	10.0	15.1	16.7	23.2	12.3	22.9
30	21.1	15.4	17.3	26.2	30.4	22.3	21.7	40.7
45	26.8	11.6	22.4	30.3	38.5	15.3	29.6	44.8
60	30.8	7.0	26.8	34.0	43.1	9.2	35.9	47.1
75	34.2	5.0	31.5	36.8	46.1	5.3	41.1	49.2
90	36.9	3.2	35.1	38.8	48.3	3.3	44.6	50.2
105	39.6	3.3	37.3	41.2	49.8	2.4	47.3	51.3
120	41.9	3.3	39.4	44.2	51.1	2.3	48.3	52.7
240	57.0	1.8	55.7	58.9	60.8	2.0	58.9	63.6
480	80.6	1.6	78.4	83.7	77.2	1.3	75.7	78.7

All references cited herein are hereby incorporated by reference. The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that further drugs can be included, and that the shapes, components, additives, proportions, methods of formulation, and other parameters described herein can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed:

1. A pharmaceutical composition comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and about 1.5 mg to about 4.0 mg oxycodone or a pharmaceutically acceptable salt thereof; and

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(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 10 mg, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 100 rpm in 900 mL of 0.1N HCl using a USP type II apparatus at a constant temperature of about 37° C., about 25% to about 35% of the total amount of oxycodone or salt thereof in the composition is released at about 15 minutes in the test and about 50% to about 55% of the total amount of acetaminophen in the composition is released at about 15 minutes in the test.

2. The pharmaceutical composition of claim 1,

wherein upon oral administration of a single dose of the composition to a subject, the composition provides a C_{max} for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg, a C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg, a T_{max} for oxycodone from about 2 hours to about 7 hours, and a T_{max} for acetaminophen from about 0.5 hour to about 6 hours.

3. The pharmaceutical composition of claim 1, wherein from about 50% to about 65%, by weight, of the oxycodone or salt is released from the composition at about 2 hours in the test, from about 70% to about 85%, by weight, of the oxycodone or salt is released from the composition at about 4 hours in the test, from about 90% to about 100%, by weight, of the oxycodone or salt is released from the composition at about 8 hours in the test, from about 60% to about 75%, by weight, of the acetaminophen is released from the composition at about 2 hours in the test, and from about 75% to about 85%, by weight, of the acetaminophen is released from the composition at about 4 hours in the test.

4. The pharmaceutical composition of claim 1, wherein upon oral administration of multiple doses to a subject in need of analgesia, the composition produces a blood plasma profile characterized by a mean AUC for oxycodone from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, a steady state AUC for oxycodone from about 13.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, a mean AUC for acetaminophen from about 35.0 ng·hr/mL/mg to about 80.0 ng·hr/mL/mg, and a steady state AUC for acetaminophen from about 37.0 ng·hr/mL/mg to about 42.0 ng·hr/mL/mg.

5. The pharmaceutical composition of claim 1, wherein upon oral administration of multiple doses to a subject in need of analgesia, the composition produces a blood plasma profile characterized by a median T_{max} for oxycodone from about 3.0 hours to about 6.0 hours, a steady state T_{max} for oxycodone from about 2.0 hours to about 3.0 hours, a median T_{max} for acetaminophen from about 1.0 hour to about 5.0 hours, and a steady state T_{max} for acetaminophen from about 0.5 hour to about 1.0 hours.

6. The pharmaceutical composition of claim 1, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 100 rpm in 900 mL of 0.1N HCl using a USP type II apparatus at a constant temperature of about 37° C., about 34% to about 40% of the oxycodone or salt thereof is released at about 30 minutes in the test and about 51% to about 58% of the acetaminophen is released at about 30 minutes in the test.

7. The pharmaceutical composition of claim 1, wherein the extended release component comprises polyethylene oxide.

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8. The pharmaceutical composition of claim 7, wherein the polyethylene oxide has a molecular weight from about 500,000 Daltons to about 10,000,000 Daltons.

9. The pharmaceutical composition of claim 1, wherein the at least one immediate release portion comprises from about 20% to about 30% of the total amount of oxycodone in the composition and from about 40% to about 60% of the total amount of acetaminophen in the composition, and the at least one extended release portion comprises the balance of each of oxycodone and acetaminophen.

10. The pharmaceutical composition of claim 1, wherein the immediate release portion comprises, by weight of the immediate release portion, from about 70% to about 80% acetaminophen and from about 0.5% to about 1% of oxycodone; and the extended release portion comprises, by weight of the extended release portion, from about 30% to about 50% of the extended release component, from about 20% to about 40% of acetaminophen, and from about 0.5% to about 2% of oxycodone.

11. The pharmaceutical composition of claim 1, wherein the extended release component comprises a polymer selected from the group consisting of linear, branched, dendrimeric, or star polymers, hydrophilic polymers, and mixtures thereof.

12. The pharmaceutical composition of claim 1, wherein the extended release component comprises a polymer selected from the group consisting of a polyalkylene oxide, poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide) poly(propylene oxide), methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, microcrystalline cellulose, acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, aminoethyl acrylate, maleic anhydride copolymer, polymaleic acid, poly(acrylamide), poly(methacrylamide), poly(dimethylacrylamide), poly(N-isopropylacrylamide), poly(olefinic alcohol), poly(vinyl alcohol), poly(N-vinyl lactam), poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), polyol, glycerol, polyglycerol, propylene glycol, trimethylene glycol, mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, mono- and di-polyoxyethylated trimethylene glycol, polyoxyethylated sorbitol, polyoxyethylated glucose, polyoxazolines, poly(methyloxazoline), poly(ethyloxazoline), polyvinylamine, polyvinylacetate, ethylene-vinyl acetate copolymer, polyvinyl acetate phthalate, polyimines, polyethyleneimine, starch, starch-based polymer, polyurethane hydrogel, chitosan, polysaccharide gums, xanthan gum, zein, shellac, ammoniated shellac, shellac-acetyl alcohol, shellac n-butyl stearate, and mixtures thereof.

13. A pharmaceutical composition comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and about 1.5 mg to about 4.0 mg oxycodone or a pharmaceutically acceptable salt thereof; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 10 mg;

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 150 rpm in 900 mL of 0.1N HCl using a USP type II apparatus at a constant temperature

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of about 37° C., the drug release profile substantially corresponds to the following:

after 15 minutes, no more than about 35%, by weight, of the total amount of the oxycodone or salt is released and no more than about 55%, by weight, of the total amount of the acetaminophen is released;

after 1 hour, no more than about 50%, by weight, of the total amount of the oxycodone or salt is released and no more than about 63%, by weight, of the total amount of the acetaminophen is released;

after 2 hours, no more than about 65%, by weight, of the total amount of the oxycodone or salt is released and no more than about 75%, by weight, of the total amount of the acetaminophen is released;

after 4 hours, from about 65% to about 85%, by weight, of the total amount of the oxycodone or salt is released and from about 70% to about 90%, by weight, of the total amount of the acetaminophen is released;

after 8 hours, from about 85% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 85% to about 100%, by weight, of the total amount of the acetaminophen is released; and

after 12 hours, from about 95% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 90% to about 100%, by weight, of the total amount of the acetaminophen is released.

14. The pharmaceutical composition of claim 13, wherein the composition comprises about 325 mg of acetaminophen and about 7.5 mg of oxycodone.

15. The pharmaceutical composition of claim 13, wherein when orally administered to a subject, the composition produces a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of oxycodone and acetaminophen.

16. The pharmaceutical composition of claim 15, wherein the biphasic increase in blood plasma concentrations of oxycodone is characterized by a plasma concentration-time profile for oxycodone in which the slope of a line drawn between 0 hour and about 2 hours is greater than the slope of a line drawn between about 2 hours and about 5 hours.

17. A pharmaceutical composition as a solid oral dosage form comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and about 1.5 mg to about 4.0 mg oxycodone or a pharmaceutically acceptable salt thereof; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is about 325 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg;

wherein upon oral administration of two solid oral dosage forms of the composition in multiple doses in an amount of about 15 mg oxycodone or salt and about 650 mg acetaminophen, the composition provides an $AUC_{0-1.7h}$ for acetaminophen of about 5.0 ng·h/mL/mg to about 13.0 ng·h/mL/mg; an $AUC_{1.7-48h}$ for acetaminophen of about 25.0 ng·h/mL/mg to about 75.0 ng·h/mL/mg, an $AUC_{0-2.8h}$ for oxycodone or salt of about 1.0 ng·h/mL/mg to about 3.0 ng·h/mL/mg; and $AUC_{2.8-48h}$ of about 7.5 ng·h/mL/mg to about 15.0 ng·h/mL/mg.

18. The pharmaceutical composition of claim 17 wherein the AUC_{0-1hr} for acetaminophen is from about 1.25 ng·hr/mL/mg to about 3.25 ng·hr/mL/mg.

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19. The pharmaceutical composition of claim 17 wherein the AUC_{0-2hr} for acetaminophen is from about 4.25 ng·hr/mL/mg to about 8.75 ng·hr/mL/mg.

20. The pharmaceutical composition of claim wherein the AUC_{0-4hr} for acetaminophen is from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg. 5

21. The pharmaceutical composition of claim 17 wherein the AUC_{0-2hr} for oxycodone is from about 0.65 ng·hr/mL/mg to about 1.35 ng·hr/mL/mg.

22. The pharmaceutical composition of claim 17 wherein the AUC_{0-4hr} for oxycodone is from about 2.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg. 10

23. A pharmaceutical composition as a solid oral dosage form for oral administration useful in the treatment of pain and for reducing the risk of acetaminophen-induced hepatic damage, comprising: 15

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and about 1.5 mg to about 4.0 mg oxycodone or a pharmaceutically acceptable salt thereof; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or salt thereof, and an extended release component; 20

wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 10 mg; and

wherein upon oral administration of two solid oral dosage forms of the composition in an amount of about 15 mg oxycodone or salt and about 650 mg acetaminophen the 25 30

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composition maintains a therapeutic blood plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hours to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration.

24. The pharmaceutical composition of claim 23, wherein upon oral administration depleted stores of hepatic glutathione are able to be substantially replenished during the later part of a dosing interval when plasma concentrations of acetaminophen are reduced.

25. The pharmaceutical composition of claim 23, wherein the AUC_{Tmax-t} for acetaminophen is from about 20.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg.

26. The pharmaceutical composition of claim 23, wherein the $AUC_{(1.7-48)}$ for acetaminophen is from about 25.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg.

27. The pharmaceutical composition of claim 1, wherein the composition is administered to a subject as bilayer tablet.

28. The pharmaceutical composition of claim 27, wherein a single dose comprises two bilayer tablets.

29. The solid oral dosage form of claim 17, wherein the solid oral dosage form is a tablet of capsule.

30. The solid oral dosage form of claim 23, wherein the solid oral dosage form is used in the treatment of acute pain.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,658,631 B1
APPLICATION NO. : 13/473563
DATED : February 25, 2014
INVENTOR(S) : Devarakonda et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

- Column 61, after Chart 1 insert --* All weights in mg.--.
- Column 72, line 64, in Table 3, “(6)” should read “(%)”.
- Column 73, line 7, in Table 3, “(6)” should read “(%)”.
- Column 76, line 27, in Table 6, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 76, line 65, in Table 7, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 77, line 35, in Table 8, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 78, line 27, in Table 9, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 78, line 65, in Table 10, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 79, line 35, in Table 11, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 82, line 28, in Table 15, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.

Signed and Sealed this
Twenty-fourth Day of June, 2014



Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

Page 2 of 2

U.S. Pat. No. 8,658,631 B1

- Column 82, line 65, in Table 16, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 83, line 35, in Table 17, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 84, line 25, in Table 18, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 84, line 65, in Table 19, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 85, line 37, in Table 20, “^bAUC from zero the median T_{\max} ...” should read “^bAUC from zero to the median T_{\max} ...”.
- Column 90, line 36, in Table 25, “^{hr} N = 17” should read “^h N = 17”.
- Column 99, line 44, in Table 38, “6.88 (2.15)⁶” should read “6.88 (2.15)^b”.
- Column 118, line 40, in Table 55, “oxycodone HCl” should read “oxycodone HCl”.
- Column 118, line 42, in Table 55, “oxycodone HCl” should read “oxycodone HCl”.
- Column 119, line 2, in Table 55, “oxycodone HCl” should read “oxycodone HCl”.
- Column 119, line 4, in Table 55, “oxycodone HCl” should read “oxycodone HCl”.

In the Claims

- Column 124, line 63, in Claim 17, insert --for oxycodone or salt-- after “ $AUC_{2.8-48h}$ ”.
- Column 125, line 4, in Claim 20, insert --17-- after “of claim”.
- Column 126, line 20, in Claim 26, replace “ $AUC_{(1.7-48)}$ ” with “ $AUC_{(1.7-48hr)}$ ”.
- Column 126, line 23, in Claim 27, insert --a-- after “subject as”.
- Column 126, line 27, in Claim 29, replace “of” with “or”.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

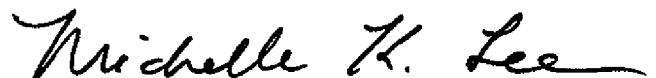
PATENT NO. : 8,658,631 B1
APPLICATION NO. : 13/473563
DATED : February 25, 2014
INVENTOR(S) : Devarakonda et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, item 75, "Michael J. Guiliani" should read "Michael J. Giuliani".

Signed and Sealed this
Twenty-sixth Day of August, 2014

A handwritten signature in black ink, reading "Michelle K. Lee". The signature is written in a cursive style with a long, sweeping underline.

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

EXHIBIT C

US008741885B1

(12) **United States Patent**
Devarakonda et al.(10) **Patent No.:** **US 8,741,885 B1**
(45) **Date of Patent:** ***Jun. 3, 2014**(54) **GASTRIC RETENTIVE EXTENDED
RELEASE PHARMACEUTICAL
COMPOSITIONS**(75) Inventors: **Krishna Devarakonda**, St. Louis, MO
(US); **Michael J Guilian**, Creve Coeur,
MO (US); **Vishal K Gupta**,
Hillsborough, NJ (US); **Ralph A**
Heasley, Webster Groves, MO (US);
Susan Shelby, Creve Coeur, MO (US)(73) Assignee: **Mallinckrodt LLC**, Hazelwood, MO
(US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 4 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **13/473,571**(22) Filed: **May 16, 2012****Related U.S. Application Data**(60) Provisional application No. 61/487,047, filed on May
17, 2011, provisional application No. 61/537,533,
filed on Sep. 21, 2011, provisional application No.
61/606,896, filed on Mar. 5, 2012.(51) **Int. Cl.**
A61K 31/34 (2006.01)
A61K 9/22 (2006.01)(52) **U.S. Cl.**
USPC **514/183**(58) **Field of Classification Search**
USPC **514/183**
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

4,713,243 A 12/1987 Schiraldi et al.
4,851,226 A 7/1989 Julian et al.
4,894,236 A 1/1990 Jang et al.
4,996,058 A 2/1991 Sinnreich
5,075,114 A 12/1991 Roche
5,266,331 A 11/1993 Oshlack et al.
5,336,691 A 8/1994 Raffa et al.
5,478,577 A 12/1995 Sackler et al.
5,508,042 A 4/1996 Oshlack et al.
5,549,912 A 8/1996 Oshlack et al.
5,582,837 A 12/1996 Shell
5,626,874 A 5/1997 Conte et al.
5,656,295 A 8/1997 Oshlack et al.
5,672,360 A 9/1997 Sackler et al.
5,783,212 A 7/1998 Fassihi et al.
5,866,161 A 2/1999 Childers et al.
5,876,759 A 3/1999 Gowan, Jr.
5,891,471 A 4/1999 Miller et al.
5,945,123 A 8/1999 Hermelin
5,945,125 A 8/1999 Kim
5,958,459 A 9/1999 Chasin et al.
5,965,161 A 10/1999 Oshlack et al.
5,965,163 A 10/1999 Miller et al.
5,965,167 A 10/1999 Sanghvi et al.

5,968,551 A 10/1999 Oshlack et al.
5,972,389 A 10/1999 Shell et al.
5,980,882 A 11/1999 Eichman
6,024,982 A 2/2000 Oshlack et al.
6,068,855 A 5/2000 Leslie et al.
6,071,208 A 6/2000 Koivunen
6,103,219 A 8/2000 Sherwood et al.
6,103,261 A 8/2000 Chasin et al.
6,126,969 A 10/2000 Shah et al.
6,143,322 A 11/2000 Sackler et al.
6,210,714 B1 4/2001 Oshlack et al.
6,245,357 B1 6/2001 Edgren et al.
6,251,430 B1 6/2001 Zhang et al.
6,254,887 B1 7/2001 Miller et al.
6,340,475 B2 1/2002 Shell et al.
6,372,254 B1 4/2002 Ting et al.
6,375,957 B1 4/2002 Kaiko et al.
6,387,404 B2 5/2002 Oshlack et al.
6,488,962 B1 12/2002 Berner et al.
6,488,963 B1 12/2002 McGinity et al.
6,500,459 B1 12/2002 Chhabra et al.
6,599,529 B1 7/2003 Skinhoj et al.
6,635,280 B2 10/2003 Shell et al.
6,667,060 B1 12/2003 Vandecruys et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP 159852 10/1985
EP 1140026 6/2000

(Continued)

OTHER PUBLICATIONS

Ward et al., Modeling the economic and health consequences of managing chronic osteoarthritis pain with opioids in Germany: comparison of extended release oxycodone and OROS hydromorphone, Current Medical Research and Opinion, 23(10):2333-2345, 2007.*
Koizumi et al., Efficacy and Tolerability of Cancer Pain Management with Controlled-release Oxycodone Tablets in Opioid-naive Cancer Pain Patients, Starting with 5 mg Tablets, Jpn J Clin Oncol, 34(10):608-614, 2004.*
Gammaitoni et al., Effectiveness and Safety of New Oxycodone/Acetaminophen Formulations With Reduced Acetaminophen for the Treatment of Low Back Pain, Pain Medicine, 4(1):21-30, 2003.*
U.S. Appl. No. 13/360,595, filed Jan. 27, 2012, Hien-Hsuan Han et al.
U.S. Appl. No. 13/473,584, filed May 16, 2012, Devarakonda et al.
U.S. Appl. No. 13/473,578, filed May 16, 2012, Devarakonda et al.
U.S. Appl. No. 13/473,586, filed May 16, 2012, Devarakonda et al.
U.S. Appl. No. 13/473,563, filed May 16, 2012, Devarakonda et al.
Banfai B. Ganzler K, Kemeny S. Content uniformity and assay requirements in current regulations. J Chromatogr A. Jul. 13, 2007;1156(1-2):206-12. Epub Nov. 15, 2006.

(Continued)

Primary Examiner — Jeffrey S. Lundgren*Assistant Examiner* — Zenab Olabowale(74) *Attorney, Agent, or Firm* — Mayer Brown LLP(57) **ABSTRACT**

The present disclosure provides extended release pharmaceutical compositions comprising an opioid and an additional active pharmaceutical ingredient, wherein the composition exhibits gastric retentive properties which are achieved by a combination of a physical property of the composition and release of the opioid, wherein upon administration to a subject, the composition has at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

30 Claims, 66 Drawing Sheets
(48 of 66 Drawing Sheet(s) Filed in Color)

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Page 2

(56)

References Cited

U.S. PATENT DOCUMENTS

6,682,759	B2	1/2004	Lim et al.	2007/0259045	A1	11/2007	Mannion et al.
6,696,066	B2	2/2004	Kaiko et al.	2007/0275065	A1	11/2007	Oshlack et al.
6,706,281	B2	3/2004	Oshlack et al.	2007/0281018	A1	12/2007	Qiu et al.
6,723,340	B2	4/2004	Gusler et al.	2008/0020039	A1	1/2008	Parikh et al.
6,730,321	B2	5/2004	Ting et al.	2008/0031901	A1	2/2008	Qiu et al.
6,733,783	B2	5/2004	Oshlack et al.	2008/0031963	A1	2/2008	Sackler et al.
6,797,283	B1	9/2004	Edgren et al.	2008/0044482	A1	2/2008	Oshlack et al.
6,852,336	B2	2/2005	Hunter et al.	2008/0057122	A1	3/2008	Toney-Parker et al.
6,902,742	B2	6/2005	Devane et al.	2008/0113025	A1	5/2008	Devane et al.
7,074,430	B2	7/2006	Miller et al.	2008/0132532	A1	6/2008	Wright et al.
7,201,920	B2	4/2007	Kumar et al.	2008/0138422	A1	6/2008	Staniforth
7,374,781	B2	5/2008	Zhang et al.	2008/0220062	A1	9/2008	Ashton
7,405,238	B2	7/2008	Markey et al.	2009/0022798	A1	1/2009	Rosenberg et al.
7,413,751	B2	8/2008	Devane et al.	2009/0028941	A1	1/2009	Cowles et al.
7,438,927	B2	10/2008	Berner et al.	2009/0068269	A1	3/2009	Oshlack et al.
7,514,100	B2	4/2009	Oshlack et al.	2009/0081290	A1	3/2009	McKenna et al.
7,674,799	B2	3/2010	Chapman et al.	2009/0149479	A1	6/2009	Jenkins et al.
7,674,800	B2	3/2010	Chapman et al.	2009/0155357	A1	6/2009	Muhuri
7,683,072	B2	3/2010	Chapman et al.	2009/0175937	A1	7/2009	Rahmouni et al.
7,691,873	B2	4/2010	Duncalf et al.	2009/0202629	A1	8/2009	Oshlack et al.
7,776,314	B2	8/2010	Bartholomaeus et al.	2009/0304793	A1	12/2009	Boehm
7,846,476	B2	12/2010	Oshlack et al.	2009/0306119	A1	12/2009	Keane
7,897,172	B2	3/2011	Qasem et al.	2009/0311320	A1	12/2009	Oury et al.
7,939,543	B2	5/2011	Kupper	2009/0317355	A1	12/2009	Roth et al.
7,943,170	B2	5/2011	Chan et al.	2009/0324714	A1	12/2009	Liu et al.
7,976,870	B2	7/2011	Berner et al.	2010/0010030	A1	1/2010	Jain et al.
8,075,872	B2	12/2011	Arkenau-Maric et al.	2010/0015222	A1 *	1/2010	Han et al. 424/468
8,309,060	B2	11/2012	Bartholomaeus et al.	2010/0034876	A1	2/2010	Oshlack et al.
8,337,888	B2	12/2012	Wright et al.	2010/0040681	A1	2/2010	Park et al.
2001/0008639	A1	7/2001	Oshlack et al.	2010/0092570	A1	4/2010	Oshlack et al.
2002/0018810	A1	2/2002	Oshlack et al.	2010/0168148	A1	7/2010	Wright et al.
2002/0058050	A1	5/2002	Sackler et al.	2010/0172974	A1	7/2010	Oshlack et al.
2002/0192277	A1	12/2002	Oshlack et al.	2010/0172989	A1	7/2010	Roth et al.
2003/0035837	A1	2/2003	Sackler et al.	2010/0196425	A1	8/2010	Cruz et al.
2003/0044466	A1	3/2003	Markey et al.	2010/0196471	A1	8/2010	Jain et al.
2003/0091635	A1	5/2003	Baichwal et al.	2010/0196474	A1	8/2010	Han et al.
2003/0092724	A1	5/2003	Kao et al.	2010/0216829	A2	8/2010	Kumar et al.
2003/0099704	A1	5/2003	Oshlack et al.	2010/0221293	A1	9/2010	Cruz et al.
2003/0104062	A1	6/2003	Berner et al.	2010/0239662	A1	9/2010	Rahmouni et al.
2004/0096500	A1	5/2004	Oshlack et al.	2010/0260833	A1	10/2010	Bartholomaeus et al.
2004/0105887	A1	6/2004	Oshlack et al.	2011/0020451	A1	1/2011	Bartholomaeus et al.
2004/0131671	A1	7/2004	Zhang et al.	2011/0038927	A1	2/2011	Oshlack et al.
2004/0156899	A1	8/2004	Louie-Helm et al.	2011/0038930	A1	2/2011	Barnscheid et al.
2005/0013863	A1	1/2005	Lim et al.	2011/0052685	A1	3/2011	Hou et al.
2005/0020613	A1	1/2005	Boehm et al.	2011/0077238	A1	3/2011	Leech et al.
2005/0031546	A1	2/2005	Bartholomaeus et al.	2011/0117196	A1	5/2011	Gordon
2005/0089570	A1	4/2005	Cruz et al.	2011/0118189	A1	5/2011	Farr et al.
2005/0106249	A1	5/2005	Hwang et al.	2011/0129507	A1	6/2011	Cruz
2005/0112195	A1	5/2005	Cruz et al.	2011/0150969	A1	6/2011	Shah et al.
2005/0158382	A1	7/2005	Cruz et al.	2011/0150970	A1	6/2011	Shah et al.
2005/0165038	A1	7/2005	Gordon	2011/0150971	A1	6/2011	Shah et al.
2005/0232987	A1	10/2005	Srinivasan et al.	2011/0150989	A1	6/2011	Park et al.
2005/0266032	A1	12/2005	Srinivasan et al.	2011/0150990	A1	6/2011	Shah et al.
2005/0267189	A1	12/2005	Gao et al.	2011/0150991	A1	6/2011	Shah et al.
2006/0002860	A1	1/2006	Bartholomaeus et al.	2011/0159046	A1	6/2011	Cruz
2006/0057210	A1	3/2006	Oshlack et al.	2011/0166171	A1	7/2011	Qiu et al.
2006/0099255	A1	5/2006	Oshlack et al.	2011/0177168	A1	7/2011	Chan et al.
2006/0165791	A1	7/2006	Oshlack et al.	2011/0195116	A1	8/2011	Hobbs et al.
2006/0193782	A1	8/2006	Bartholomaeus et al.	2011/0195989	A1	8/2011	Rudnic et al.
2006/0205752	A1	9/2006	Whitehead	2011/0207762	A1	8/2011	Chapman et al.
2006/0240105	A1	10/2006	Devane et al.	2011/0212173	A1	9/2011	Young et al.
2006/0251721	A1	11/2006	Cruz et al.	2011/0229526	A1	9/2011	Rosenberg et al.
2006/0263436	A1	11/2006	Baert et al.	2011/0229533	A1	9/2011	Edgren et al.
2006/0269604	A1	11/2006	Sackler et al.	2011/0262532	A1	10/2011	Oshlack et al.
2006/0292214	A1	12/2006	Jenkins et al.	2011/0287095	A1	11/2011	Park et al.
2007/0020335	A1	1/2007	Chen et al.	2011/0301129	A1	12/2011	Berner et al.
2007/0048228	A1	3/2007	Arkenau-Maric et al.	2011/0318392	A1	12/2011	Cruz et al.
2007/0059359	A1	3/2007	Backensfeld et al.	2012/0321713	A1	12/2012	Han et al.
2007/0128279	A1	6/2007	Edgren et al.				
2007/0183980	A1	8/2007	Arkenau-Maric et al.				
2007/0184112	A1	8/2007	Wong et al.				
2007/0190142	A1	8/2007	Breitenbach et al.				
2007/0207200	A1	9/2007	Plachetka et al.				
2007/0237833	A1	10/2007	Sackler et al.				
2007/0259033	A1	11/2007	Cruz				

FOREIGN PATENT DOCUMENTS

WO	9718814	5/1997
WO	9855107	12/1998
WO	03024426	3/2003
WO	2005013863	2/2005
WO	2005030182	4/2005
WO	2006022759	3/2006
WO	2006071208	7/2006
WO	2008015221	2/2008

US 8,741,885 B1

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(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	2009049405	4/2009
WO	2009076764	6/2009
WO	2009114648	9/2009
WO	2009135846	11/2009
WO	2010032128	3/2010
WO	2010069050	6/2010
WO	2010078486	7/2010
WO	2010141505	12/2010
WO	2011009603	1/2011
WO	2011009604	1/2011
WO	2011068723	6/2011
WO	2011077451	6/2011
WO	2011106416	9/2011
WO	2012007159	1/2012

OTHER PUBLICATIONS

Zhu Y, Shah NH, Malick AW, Infeld MH, McGinity JW. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. *Int J Pharm.* Jul. 25, 2002; 241(2):301-10.

Nimmo, W.S. et al., "Inhibition of Gastric Emptying and Drug Absorption by Narcotic Analgesics", *Br. J. Clin. Pharmacol.*, 2:509-513 (1975).

Altat S A et al., "Bead Compacts II. Evaluation of Rapidly Disintegrating Nonsegregating Compressed Bead Formulations"; *Drug Development and Industrial Pharmacy*, New York, NY, US, vol. 25, No. 5, May 1, 1999; pp. 635-642.

International Search Report from Application No. PCT/US2010/061400 with a mailing date of Nov. 25, 2011.

Endo Pharmaceuticals Package Insert for Percocet (Oxycodone and Acetaminophen Tablets, USP); pp. 1-17.

www.fda.gov/Drugs/DrugSafety/ucm239821.htm; U.S. Department of Health & Human Services; FDA Drugs Safety Communication: Prescription Acetaminophen Products to be Limited to 325mg per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure; pp. 1-5.

Tylenol Professional Product Information (2010); McNeil Consumer Healthcare; pp. 1-59.

Oxycontin Description and Patient Information; pp. 1-32.

Cooperman et al.; "A Novel Extended-Release Formulation of Oxycodone/Acetaminophen with Abuse Deterrent Properties"; Abstract; 2pgs.

Khosla et al. "The effect of tablet size on the gastric emptying of non-disintegrating tablets" (1990), *International Journal of Pharmaceutics*, 62, R9-R11.

Khosla et al. Gastrointestinal transit of non-disintegrating tablets in fed subjects (1989), *International Journal of Pharmaceutics*, 53, 107-117.

Khosla et al. "The gastrointestinal transit of a controlled release formulation of indomethacin", (1990), *International Journal of Pharmaceutics*, 60, 191-196.

Brzezicka et al. "Dynamics of Glutathione Levels in Liver and Indicatory Enzymes in Serum in Acetaminophen Intoxication in Mice" (1989) *Polish Journal of Occupational Medicine*, vol. 2, No. 1, pp. 15-22.

Gammaitoni et al. "Randomized, Double-Blind, Placebo-Controlled Comparison of the Analgesic Efficacy of Oxycodone 10 mg/Acetaminophen 325 mg versus Controlled-Release Oxycodone 20 mg in Postsurgical Pain", (2003), *J. Clin. Pharmacol.*, 43: pp. 296-304.

Moller et al. "Time to Onset of Analgesia and Analgesic Efficacy of Effervescent Acetaminophen", (2000); *J. Clin. Pharmacol.* 40: 370-378.

Nielsen et al. "Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol", (1992), *Eur. J. Clin. Pharmacol.* 42: 261-264.

James et al., "Acetaminophen-Induced Hepatotoxicity", *The American Society for Pharmacology and Experimental Therapeutics*, (2003), vol. 31, No. 12, pp. 1499-1506.

Mirochnitchenko et al. "Acetaminophen Toxicity", *The American Society for Biochemistry and Molecular Biology, Inc.*, (1999), vol. 274, No. 15, pp. 10349-10355.

Dart et al. "Acetaminophen Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management", (2006), *Clinical Toxicology*; 44: pp. 1-18.

Bolesta et al. "Hepatotoxicity Associated with Chronic Acetaminophen Administration in Patients without Risk Factors", (2002), *The Annals of Pharmacotherapy*; Feb. 2002, Vol. 36, pp. 331-333.

Rinaldi et al. "Minireview Reactive Intermediates and the Dynamics of Glutathione Transferases" (2002); *The American Society for Pharmacology and Experimental Therapeutics*; 30: pp. 1053-1058.

Rumack et al. "Acetaminophen Hepatotoxicity: The First 35 Years", *Clinical Toxicology*, (2002); 40(1), 3-20.

Bartels et al., "Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial"; (2008); *Clinical Toxicology*; 46: 243-249.

Corcoran et al. "Role of Glutathione in Prevention of Acetaminophen-Induced Hepatotoxicity by N-Acetyl-L-Cysteine in Vivo: Studies with N-Acetyl-D-Cysteine in Mice"; *The Journal of Pharmacology and Experimental Therapeutics*; (1986); vol. 238, No. 1; pp. 54-61.

Davis et al. "Species Differences in Hepatic Glutathione Depletion, Covalent Binding and Hepatic Necrosis after Acetaminophen", *Life Sciences*, vol. 14, pp. 2099-2109.

Mitchell et al. "Acetaminophen-Induced Hepatic Necrosis. IV. Protective Role of Glutathione", *The Journal of Pharmacology and Experimental Therapeutics*; (1973), vol. 187, No. 1, pp. 211-217.

Kaplowitz et al. "Drug-Induced Liver Disease" (2003); Marcel Dekker, pp. 287-325 and pp. 345-375.

Skoglund et al. "Efficacy of paracetamol-esterified methionine versus cysteine or methionine on paracetamol-induced hepatic GSH depletion and plasma ALAT level in mice", *Biochem Pharmacol* 35; 3071-3075, (1986).

Talukder et al.; "Gastroretentive Delivery Systems: A Mini Review"; *Drug Development and Industrial Pharmacy*; 2004; pp. 1019-1028; vol. 30, No. 10.

Hou et al.; "Gastric Retentive Dosage Forms: A Review"; *Critical Review in Therapeutic Drug Carrier Systems*; 2003; pp. 462-497; 20(6).

Streubel et al. "Drug delivery to the upper small intestine window using gastroretentive technologies"; *Science Direct*; 2006; pp. 501-508; 6.

Streubel et al. "Gastroretentive drug delivery systems"; *Expert Opin. Drug Deliv.*; 2006; pp. 217-233; 3(2).

Moes, A.J.; "Gastroretentive Dosage Forms"; *Critical Reviews in Therapeutic Drug Carrier Systems*; 1993; pp. 143-195; 10(2).

Davis, Stanley, S.; "Formulation strategies for absorption windows"; *DDT*; Feb. 2005; pp. 249-257; vol. 10, No. 4.

Bardonnet et al.; "Gastroretentive dosage forms: Overview and special case of *Helicobacter pylori*"; *Journal of Controlled Release*; 2006; pp. 1-18; 111.

Foremost NF Flo Lactose, "A spray-dried mixture of crystalline and amorphous lactose", Foremost Farms USA, 1pg., Online Article downloaded from the site: http://www.foremostfarms.com/Commercial/pdfs/Specifications/TDS_NF_Lactose_316.pdf, Document created on Jan. 28, 2010.

Freed et al. "pH control on nucleophilic/electrophilic oxidation", *Int. J. Pharm.*, vol. 357, pp. 180-188 (2008).

International Search Report from related PCT Patent application No. PCT/US2009/036864 mailed Aug. 31, 2009, application now published as PCT Publication No. WO2009/114648 on Sep. 17, 2009.

Lab Basics Technical Library, Particle Size Conversion Table, Sigma-Aldrich, 3 pgs., Online Article downloaded from the site: <http://www.sigmaaldrich.com/chemistry/stockroom-reagents/learning-center/technical-library/particle-size-conversion.printerview.html> on Apr. 17, 2012.

Polyox Water-Soluble Resins, Technical Data, "Degradation of water-soluble resins", Form 326-00027-1002AMS (2002).

Polyox Water-Soluble Resins, Technical Data, "Water-soluble resin storage stability", Form 326-00044-0704MAB (2004).

US 8,741,885 B1

Page 4

(56)

References Cited

OTHER PUBLICATIONS

Waterman et al., "Stabilization of pharmaceuticals to oxidative degradation", Pharm. Dev. Tech., vol. 7, No. 1, pp. 1-32 (2002).
 Zhang et al., "Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release", Pharm. Dev. Tech., vol. 6, No. 2, pp. 131-144 (2001).
 Meert et al., A preclinical comparison between different opioids: antinociceptive versus adverse effects; Pharmacology, Biochemistry & Behavior; 80(2):309-26, Feb. 2005.
 Doteuchi et al., "Pharmacological Studies of Oxycodone Hydrochloride 1. Antinociceptive Effect and General Pharmacology"; Oyo Yakuri. 49(3); 1995; 257-273.
 Miller et al., "Physical and chemical characteristics of some high purity magnesium stearate and palmitate powders"; Intl Journal of Pharmaceutics, 23 (1985), 55-67.
 Kim, Chong-Ju, "Effects of Drug Solubility, Drug Loading, and Polymer Molecular Weight on Drug Release from Polyox Tablets", Drug Development and Industrial Pharmacy; 24(7), (1998), 645-651.

Waterman, Kenneth, C., "A Critical Review of Gastric Retentive Controlled Drug Delivery", Pharmaceutical Development and Technology, 12:1-10, (2007).
 Arora et al., "Floating Drug Delivery Systems: A Review", AAPS PharmSciTech (2005), 6(3) Article 47 E372-390.
 Klausner et al., "Novel Gastroretentive Dosage Forms: Evaluation of Gastroretentivity and Its Effect on Levodopa Absorption in Humans"; Pharmaceutical Research, Vol. 20, No. 9, Sep. 2003; pp. 1466-1473.
 Klausner, et al., "Novel levodopa gastroretentive dosage form: in-vivo evaluation in dogs", Journal of Controlled Release 88 (2003) 117-126.
 Aulton M. E. "Aulton's Pharmaceutics: The Design and Manufacture of Medicines," Elsevier Limited, Oxford, Third Edition, 2007, pp. 270-278.
 Prinderre et al., "Advances in Gastro Retentive Drug-Delivery Systems," Expert Opin. Drug. Deliv., 8(9), p. 1189-1203 (Sep. 2011).
 Berner et al., "Case Studies in Swelling Polymeric Gastric Retentive Tablets," Expert Opin. Drug. Deliv., 3(4), p. 541-548 (Jul. 2006).

* cited by examiner

U.S. Patent

Jun. 3, 2014

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US 8,741,885 B1

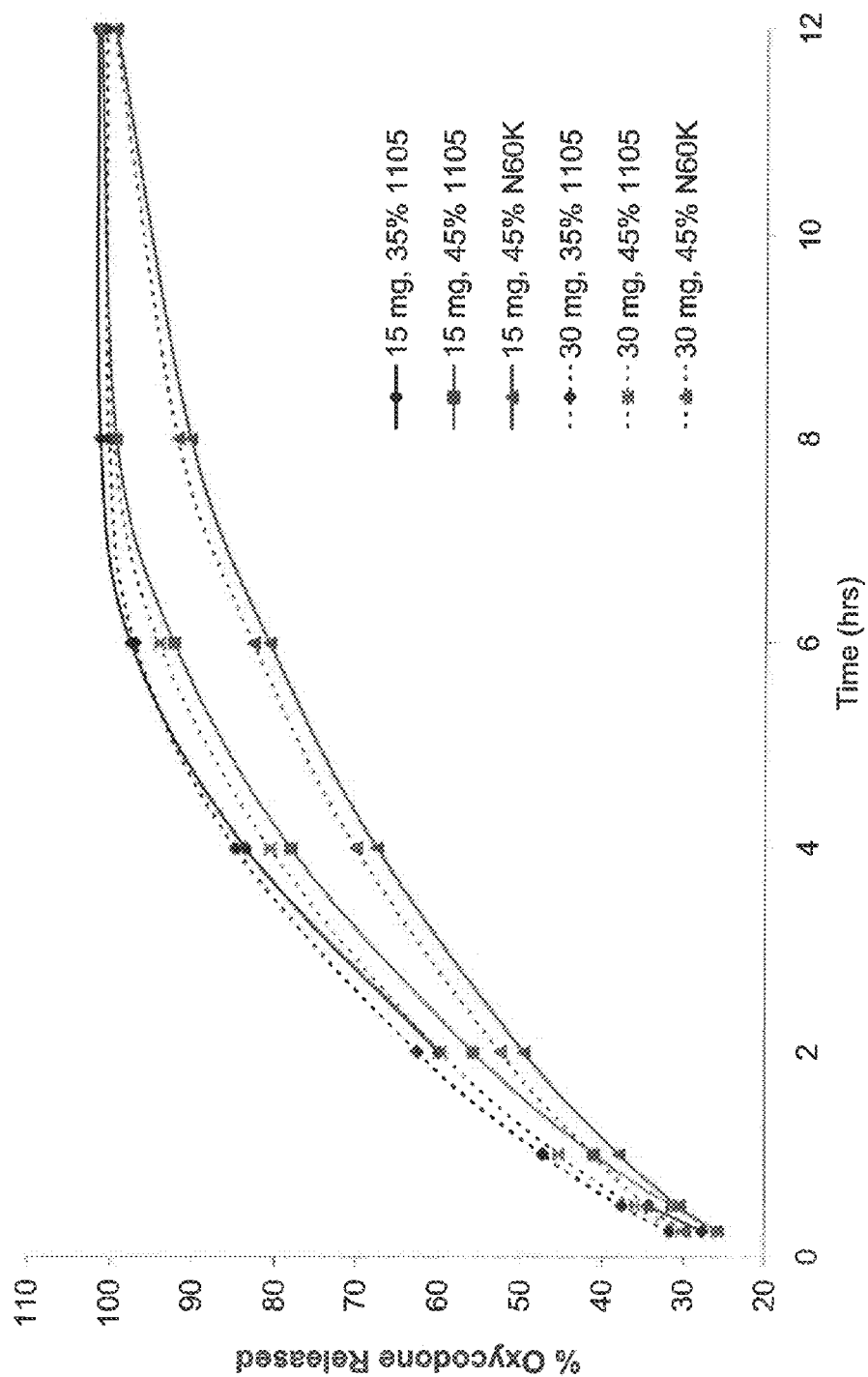


FIG. 1

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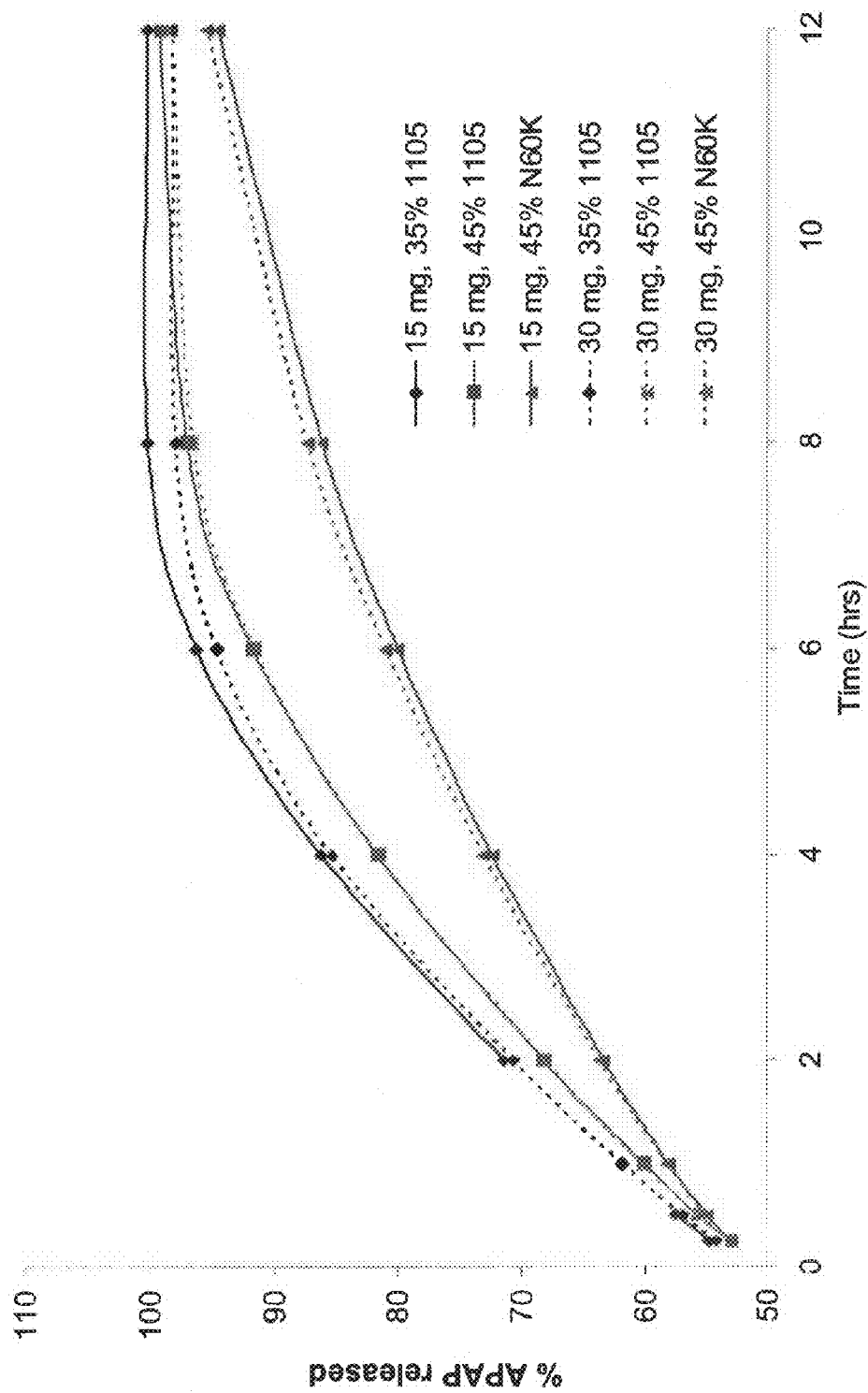


FIG. 2

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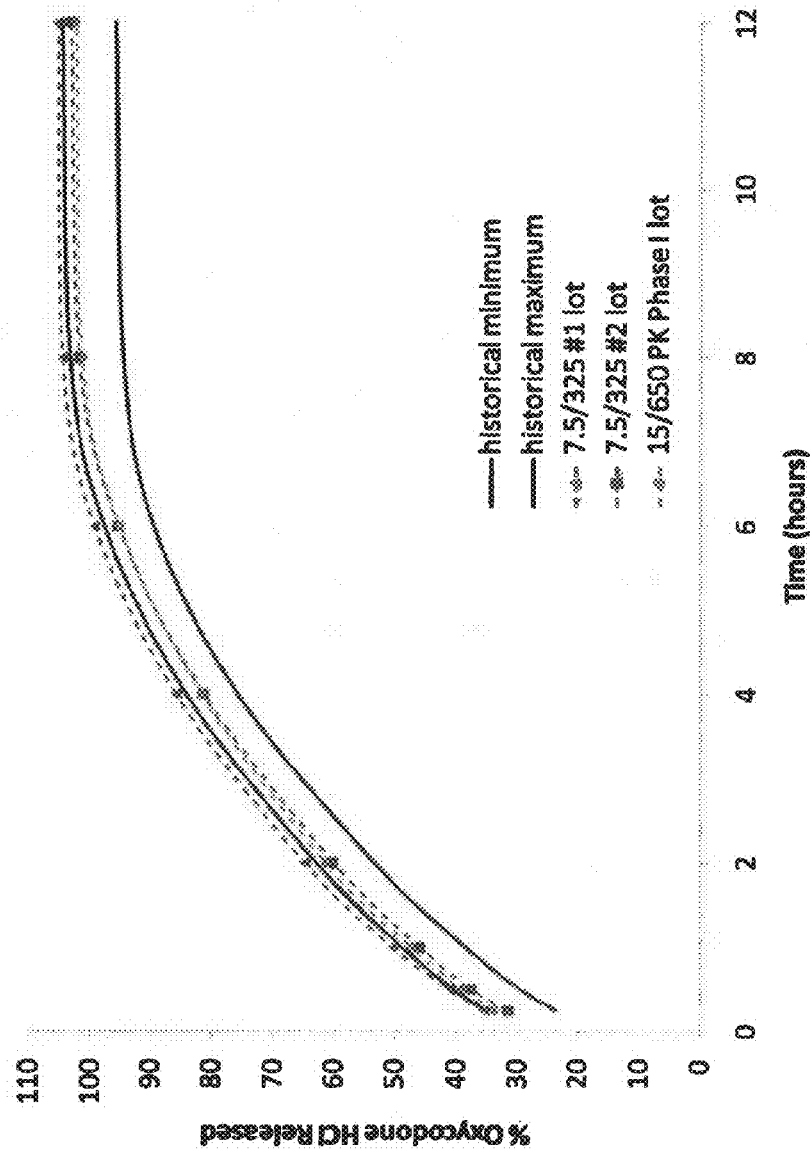


FIG. 3

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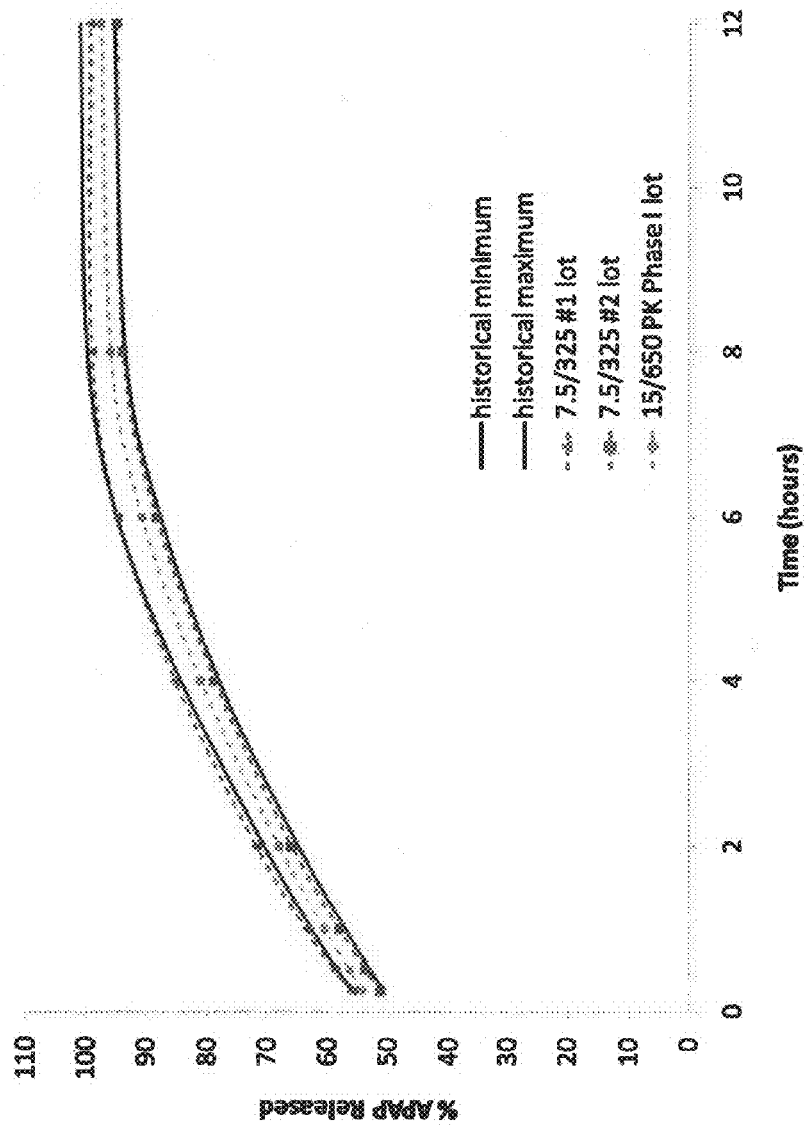


FIG. 4

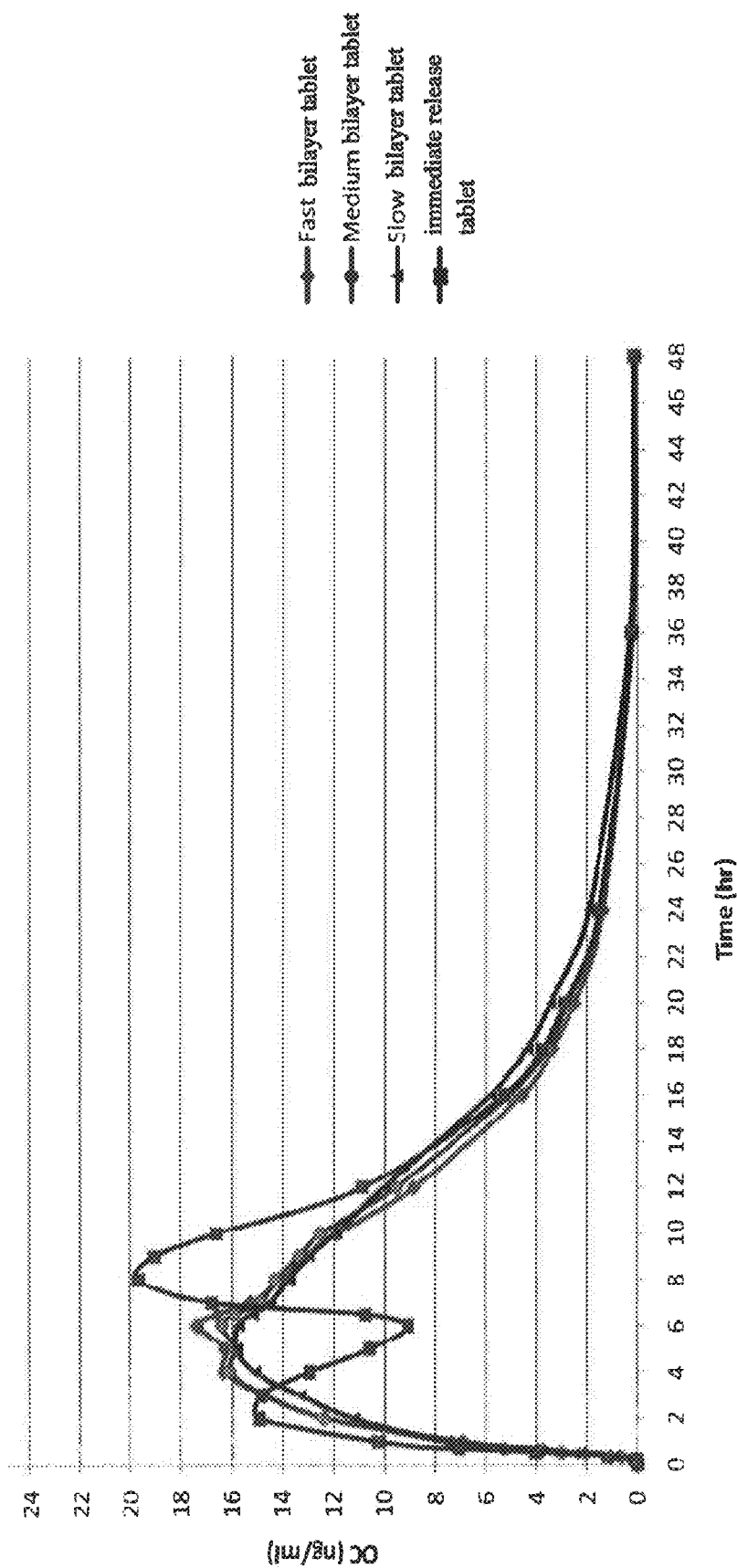


FIG. 5

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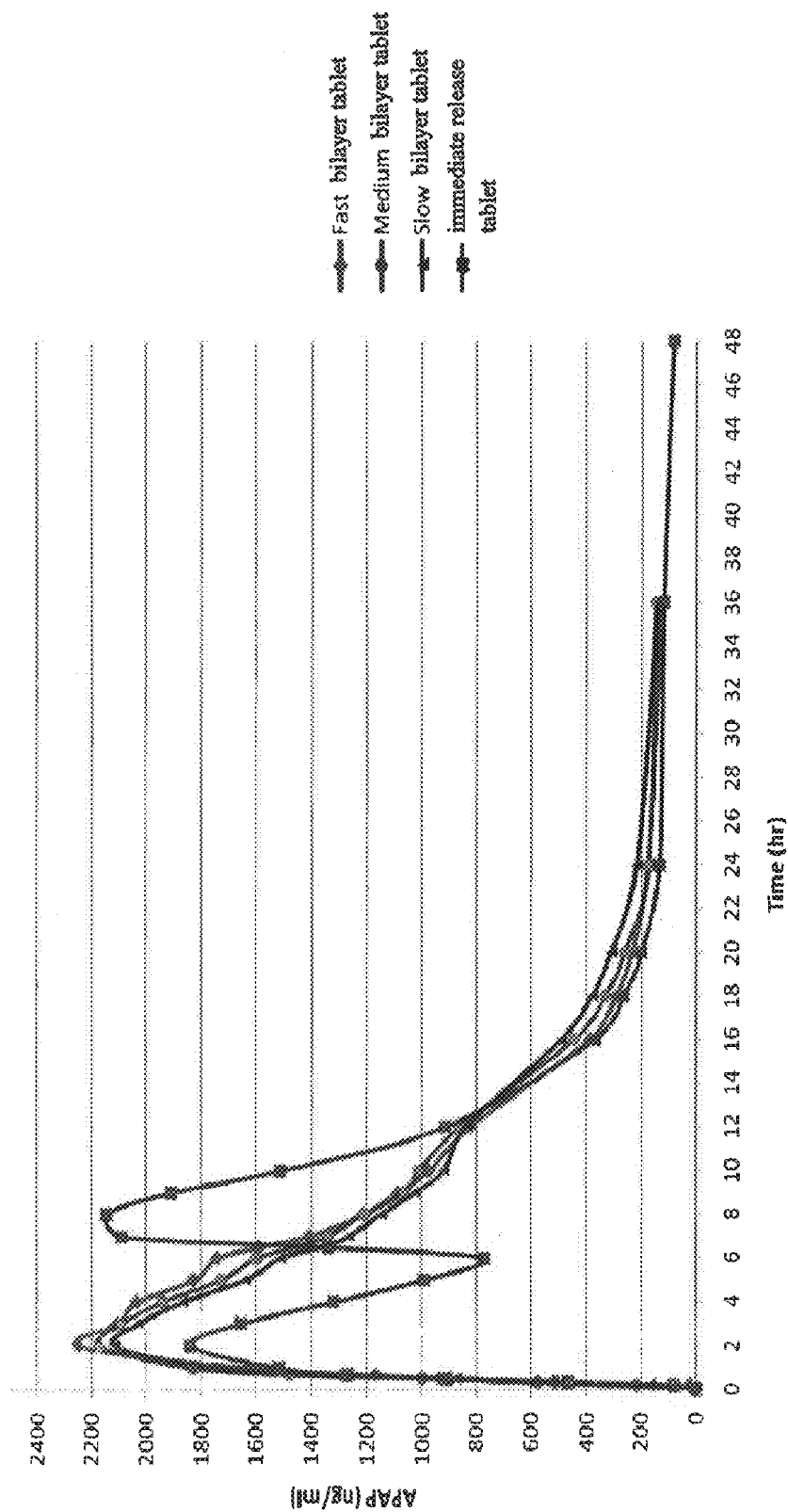


FIG. 6

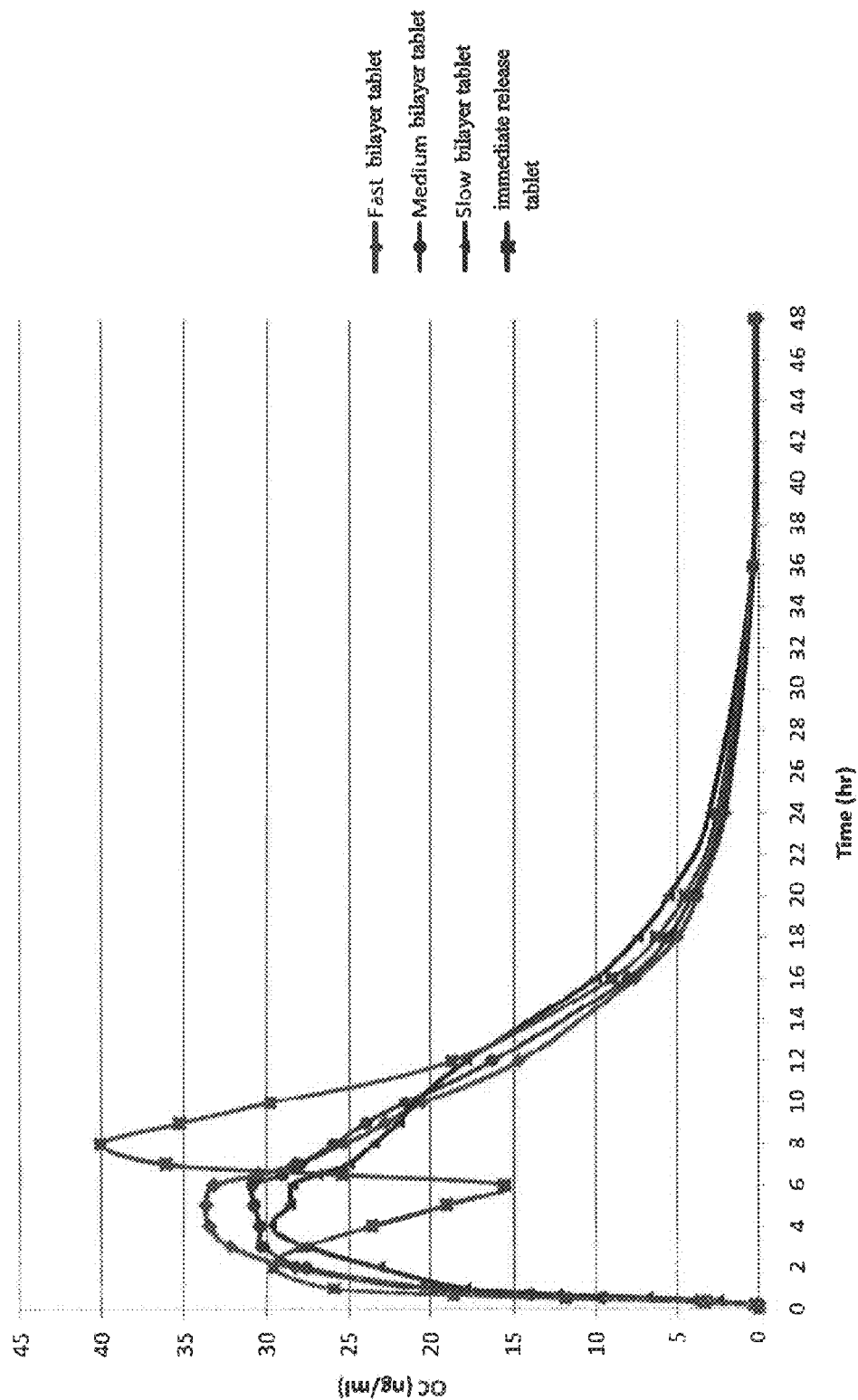


FIG. 7

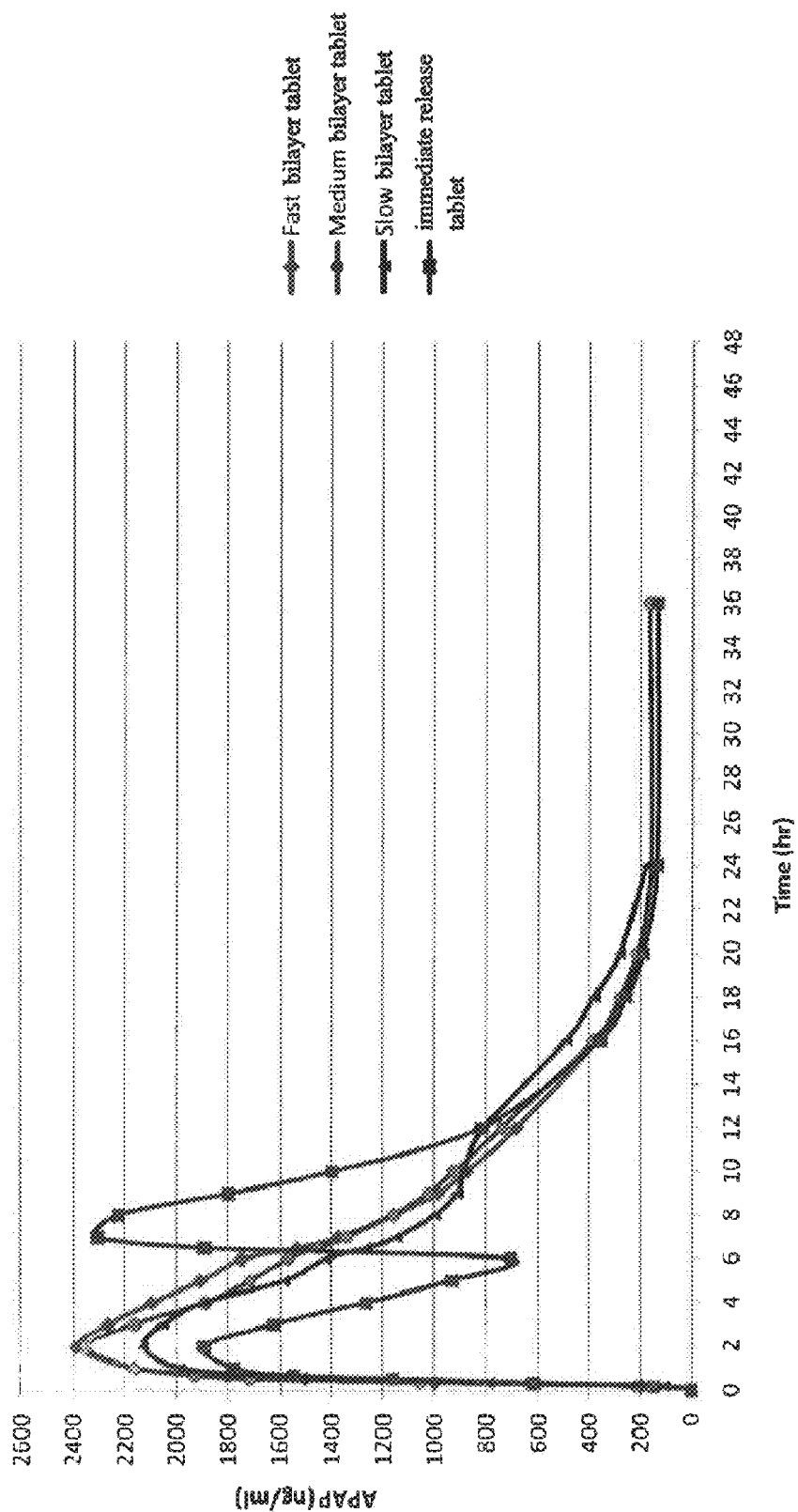


FIG. 8

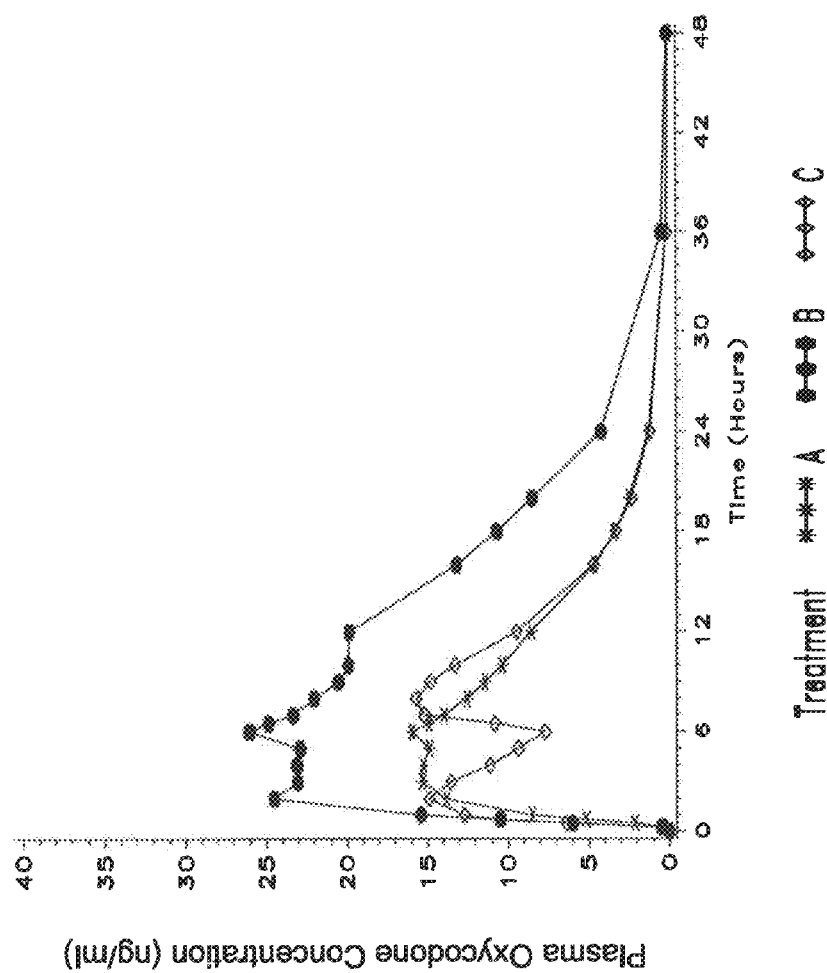


FIG. 9

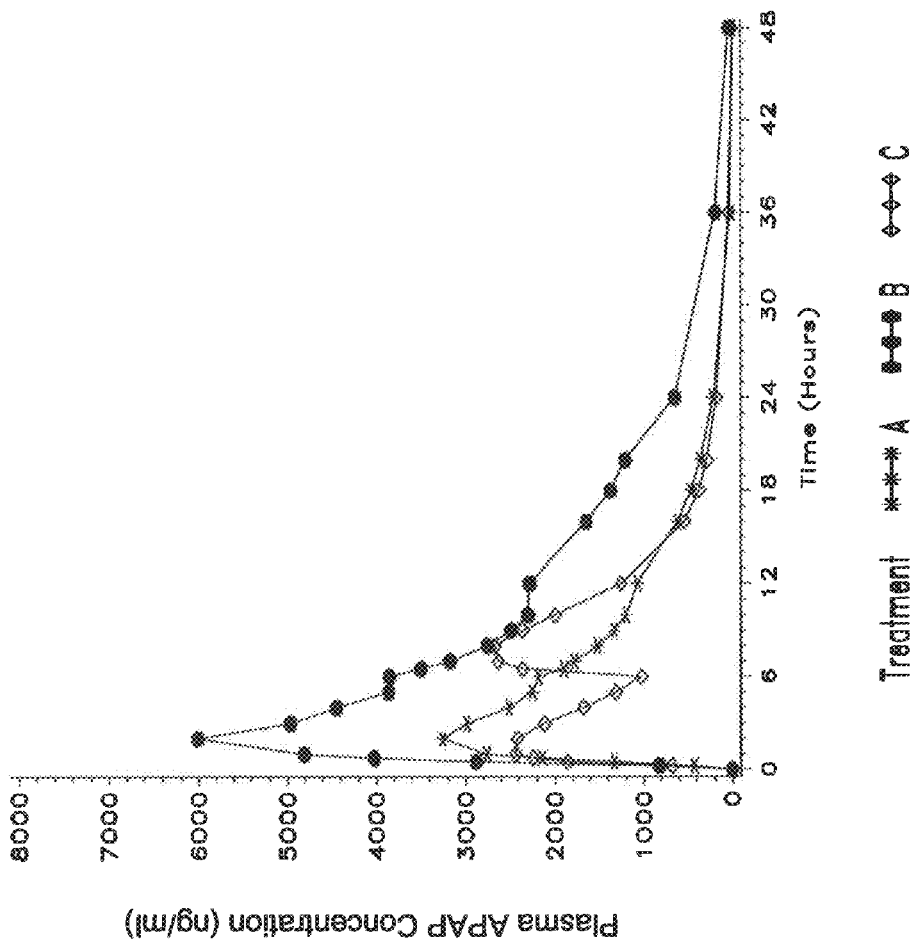


FIG. 10

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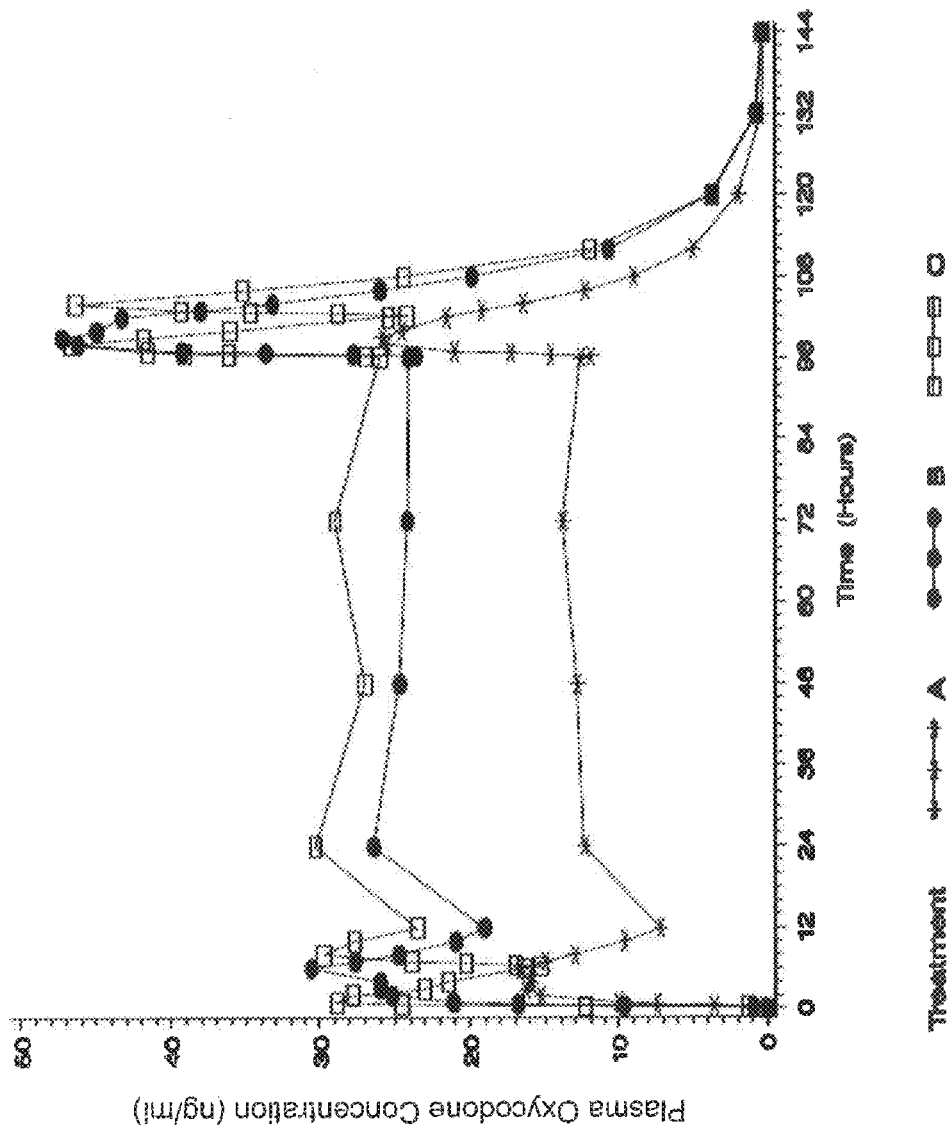


FIG. 11

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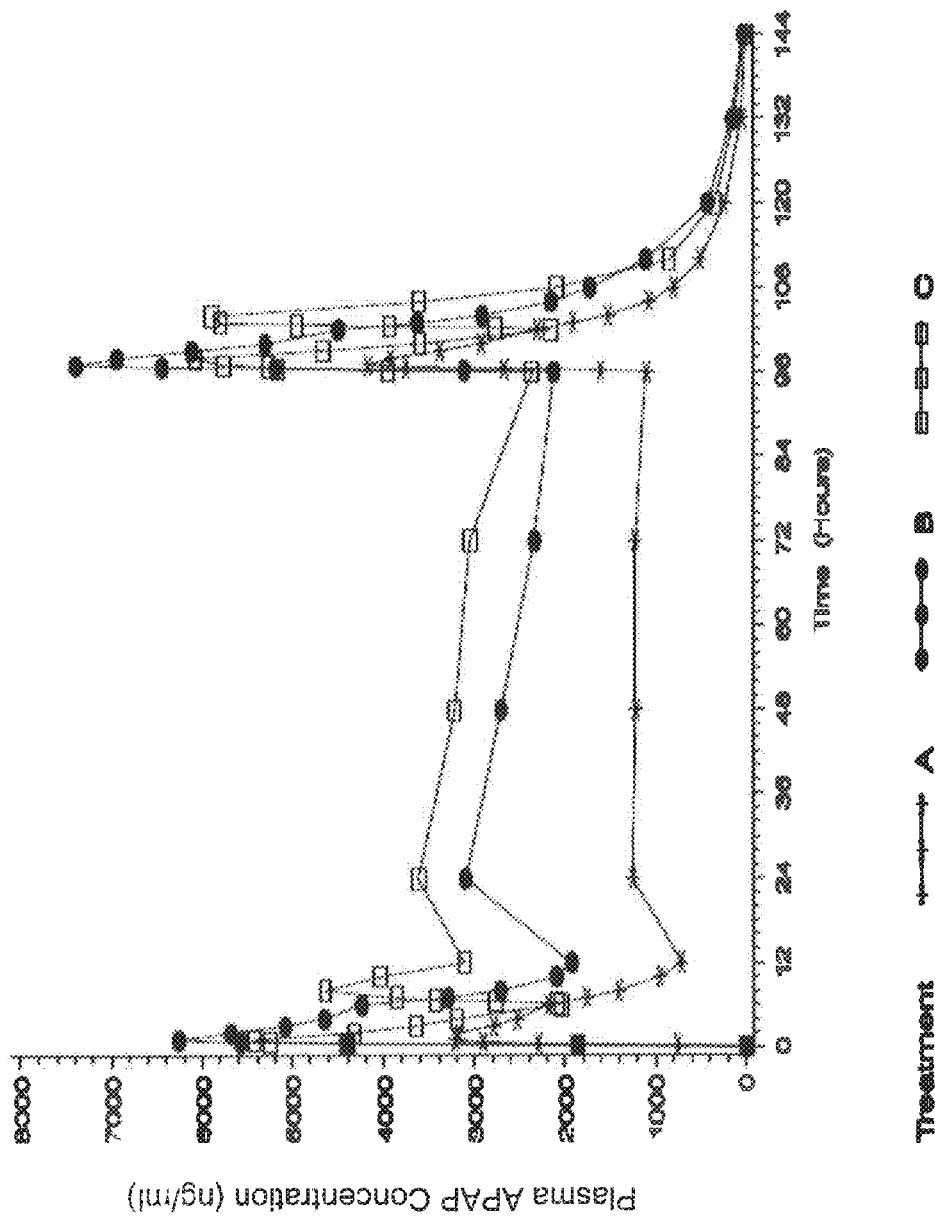


FIG. 12

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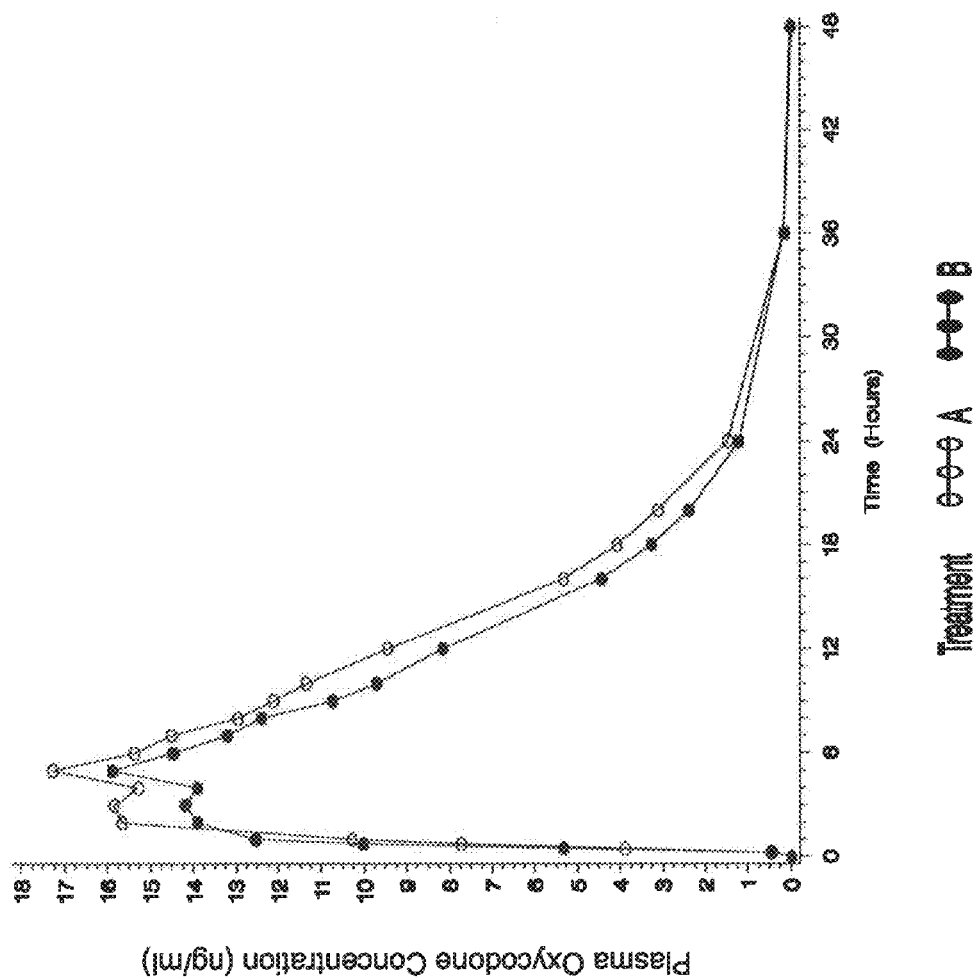


FIG. 13

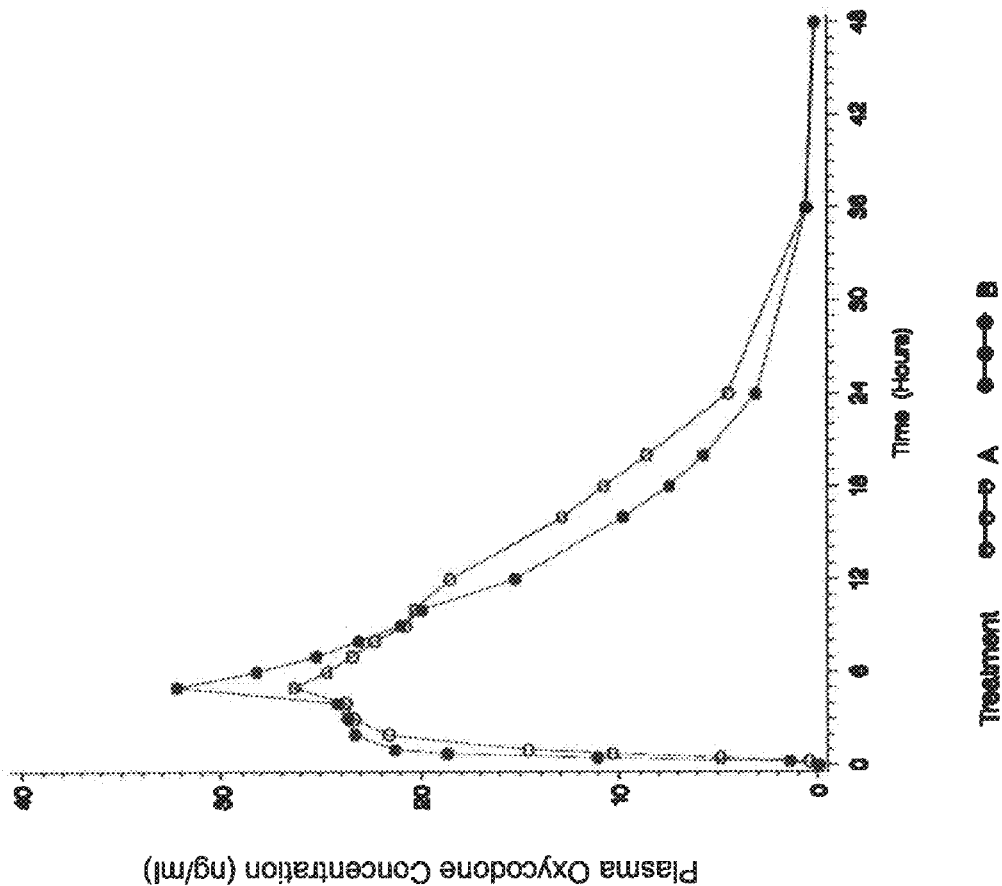


FIG. 14

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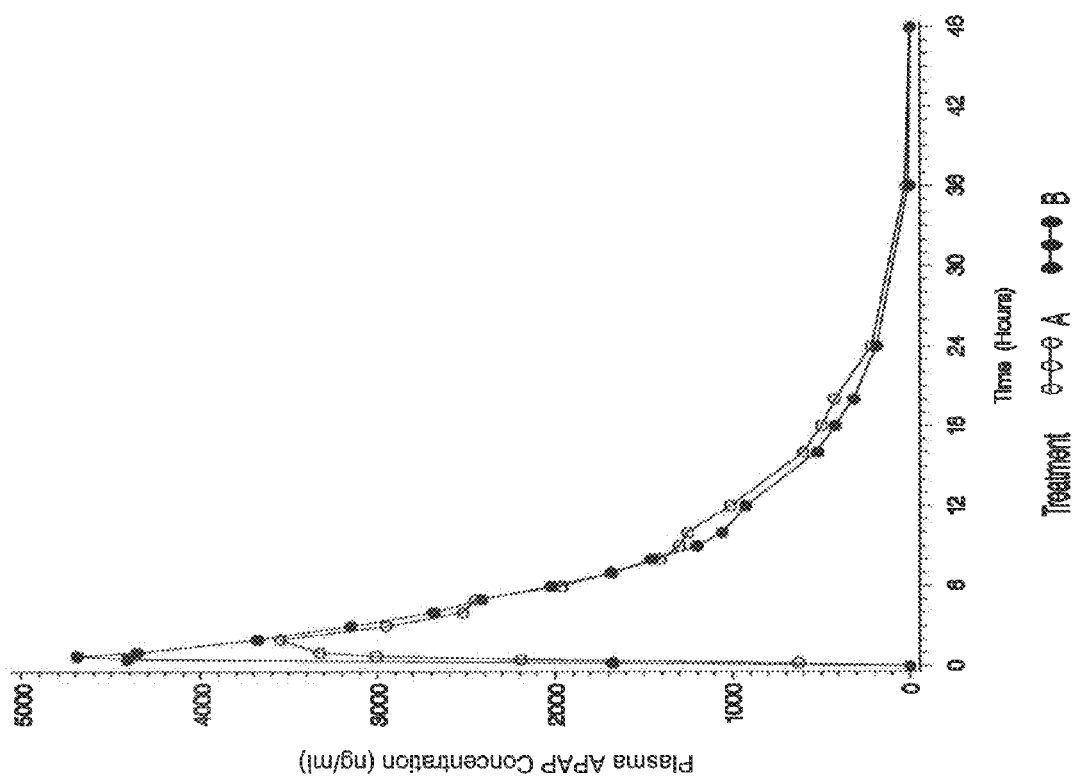


FIG. 15

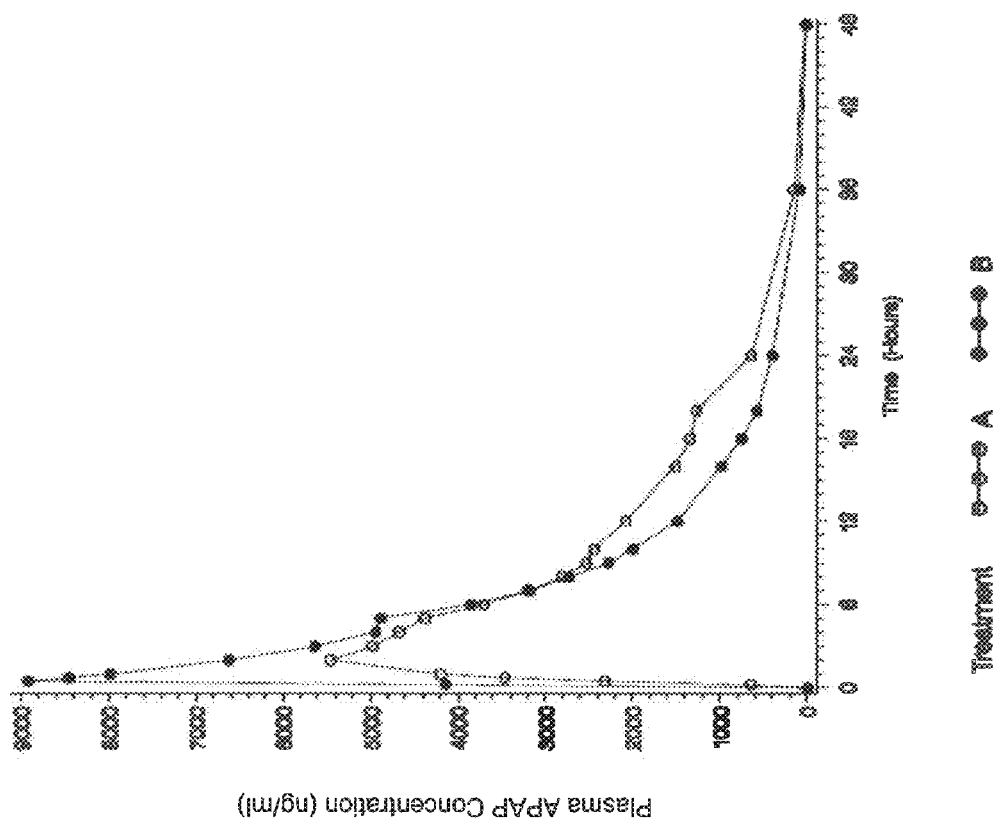


FIG. 16

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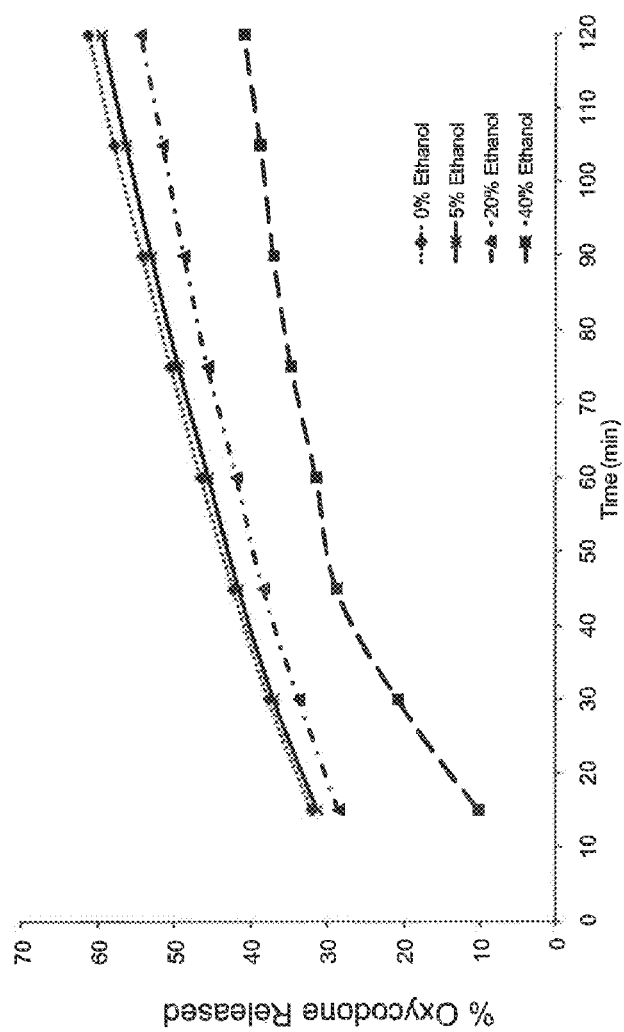


FIG. 17

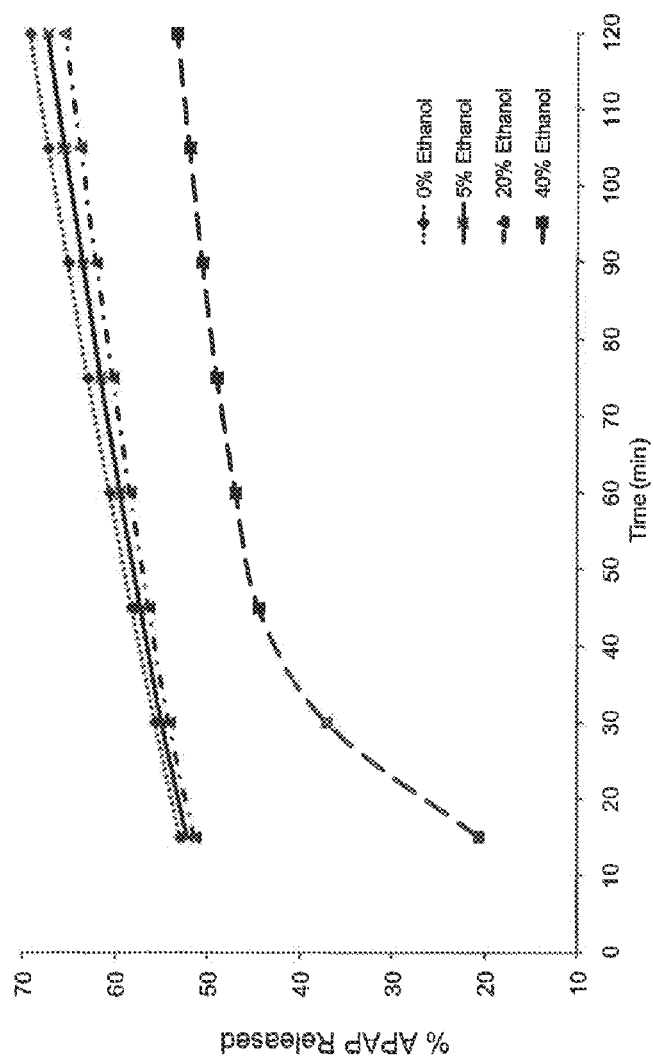


FIG. 18

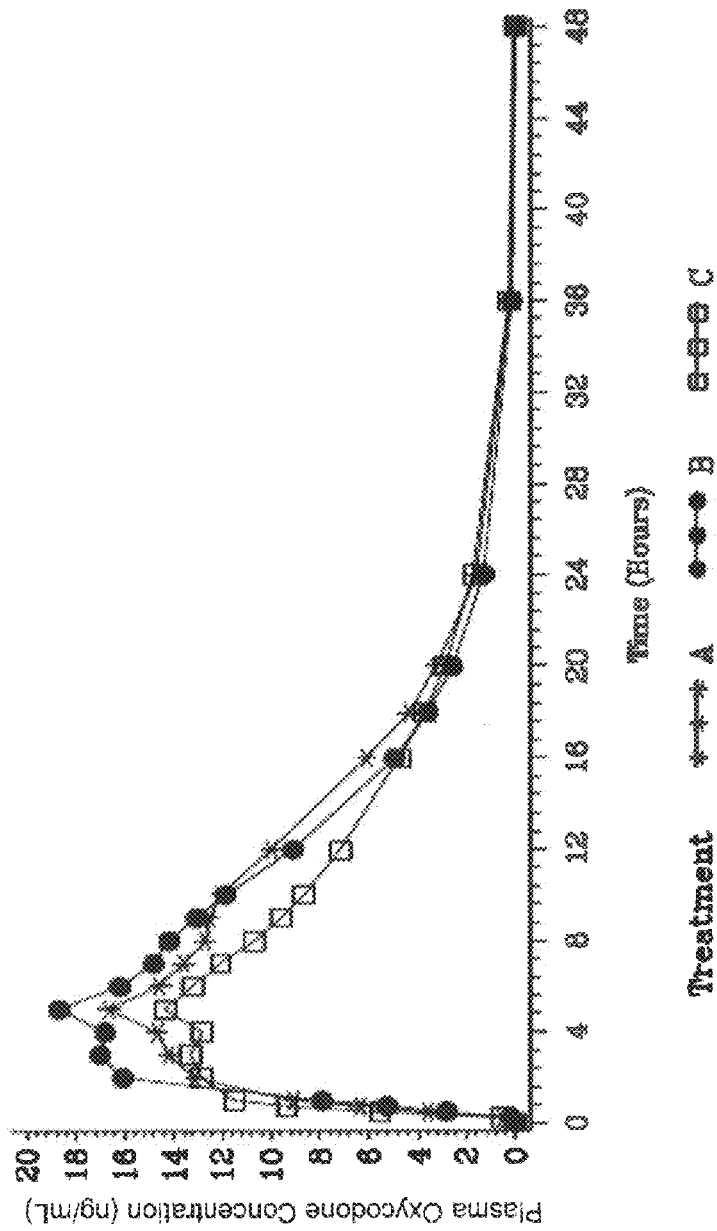


FIG. 19

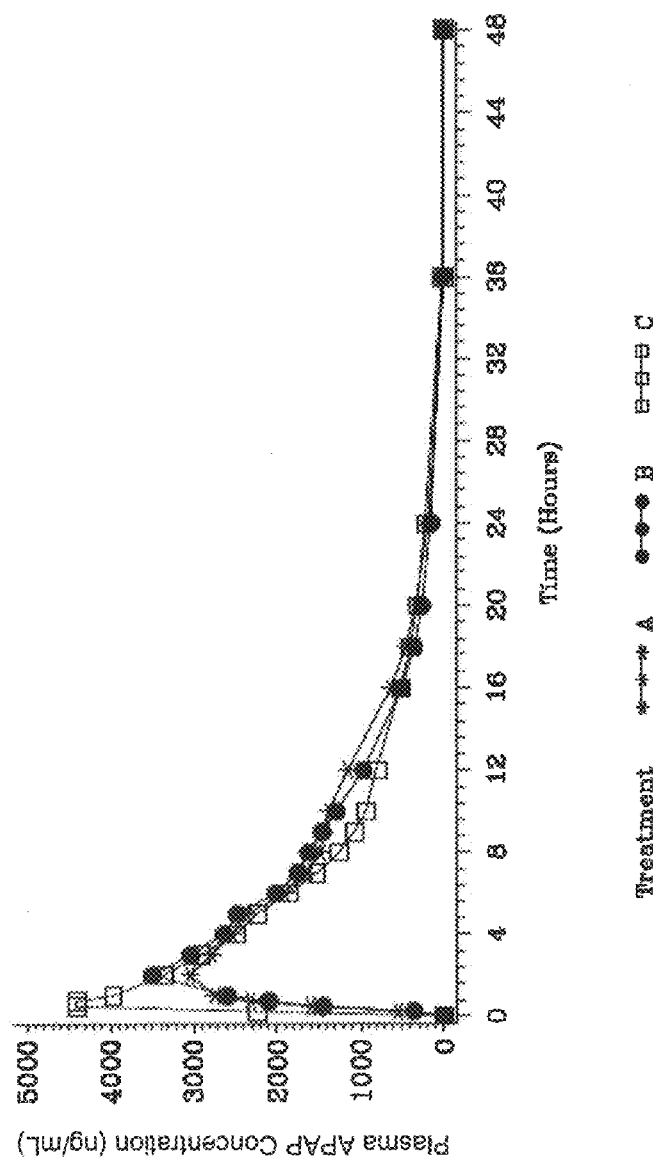


FIG. 20

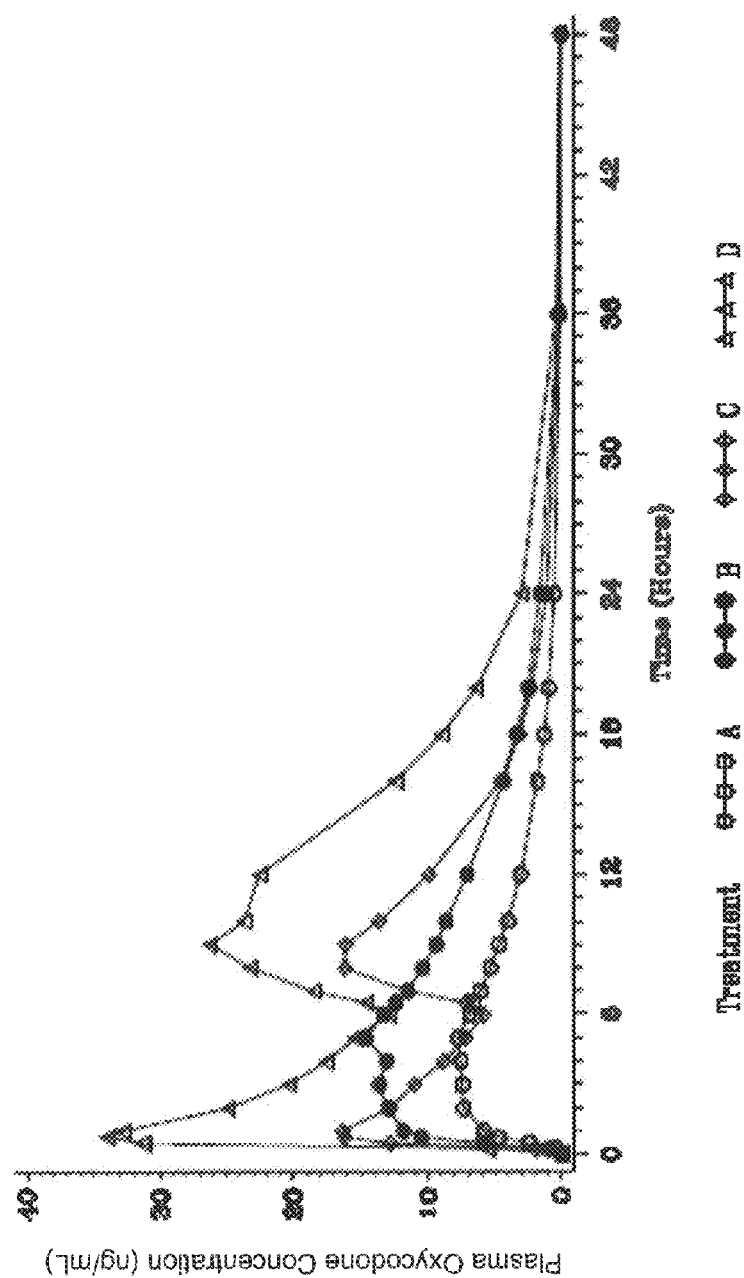


FIG. 21

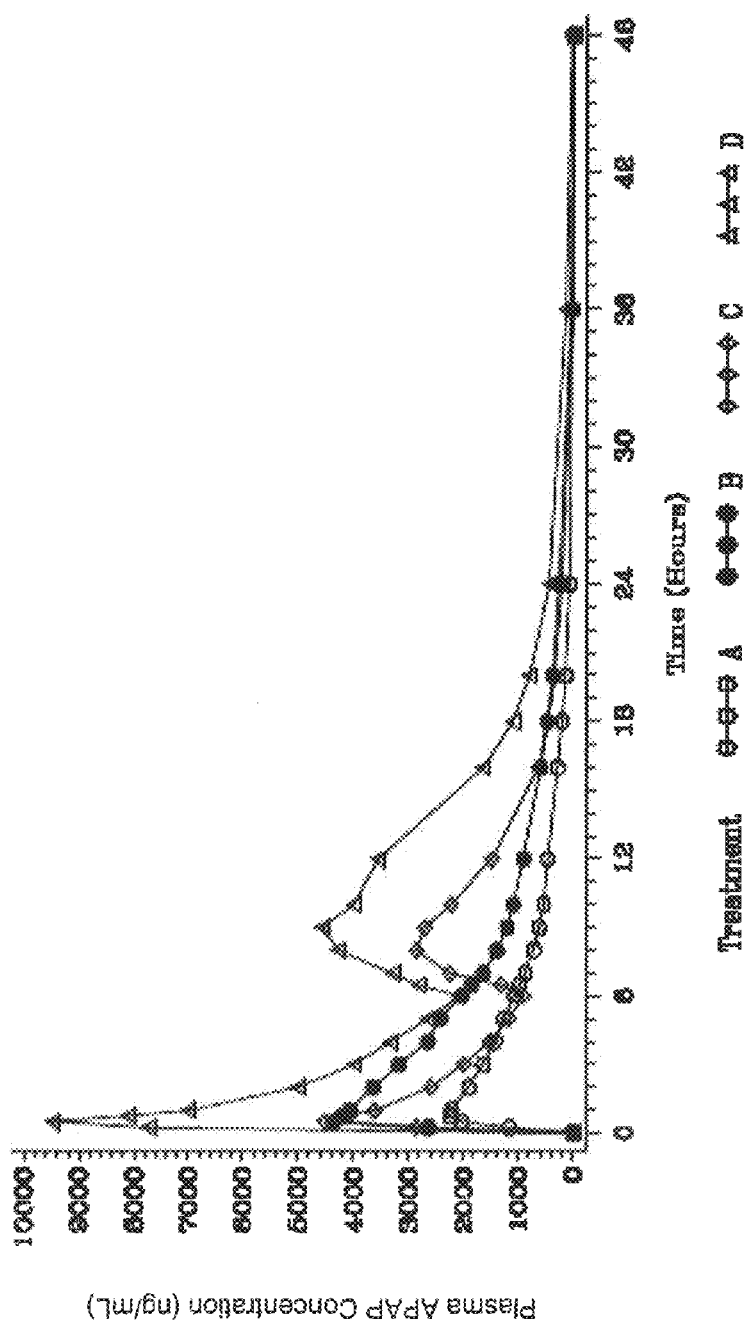


FIG. 22

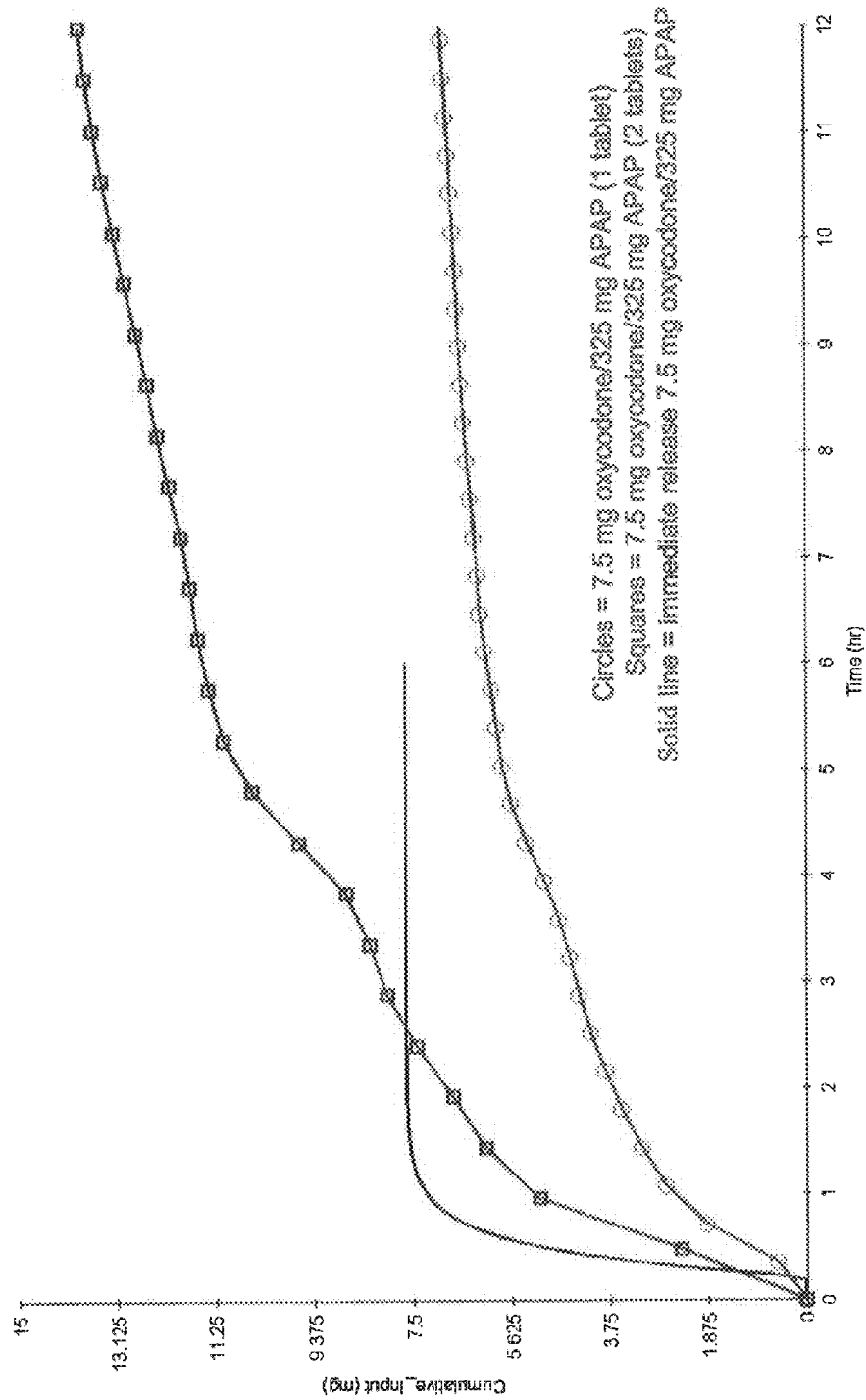


FIG. 23

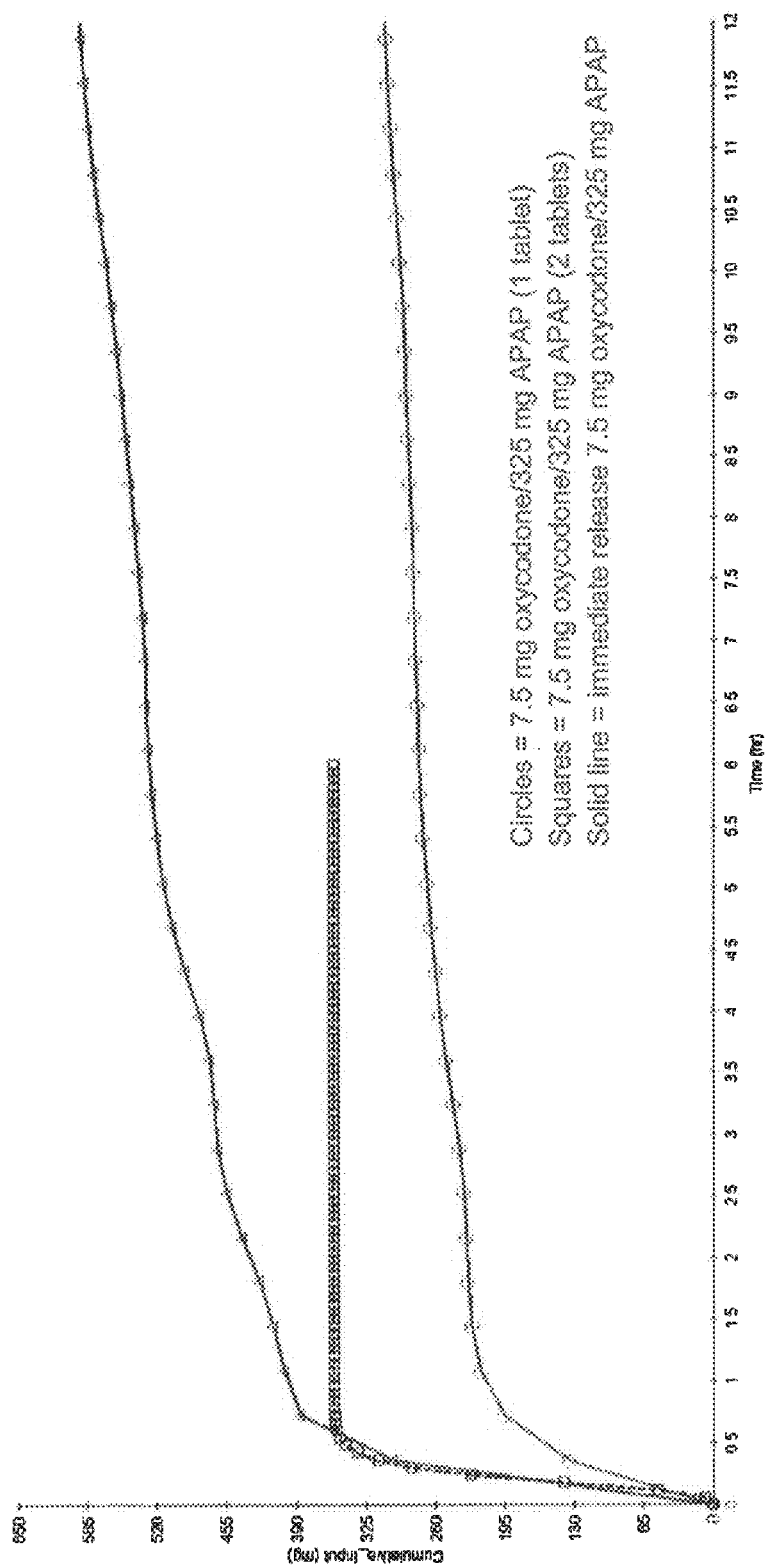


FIG. 24

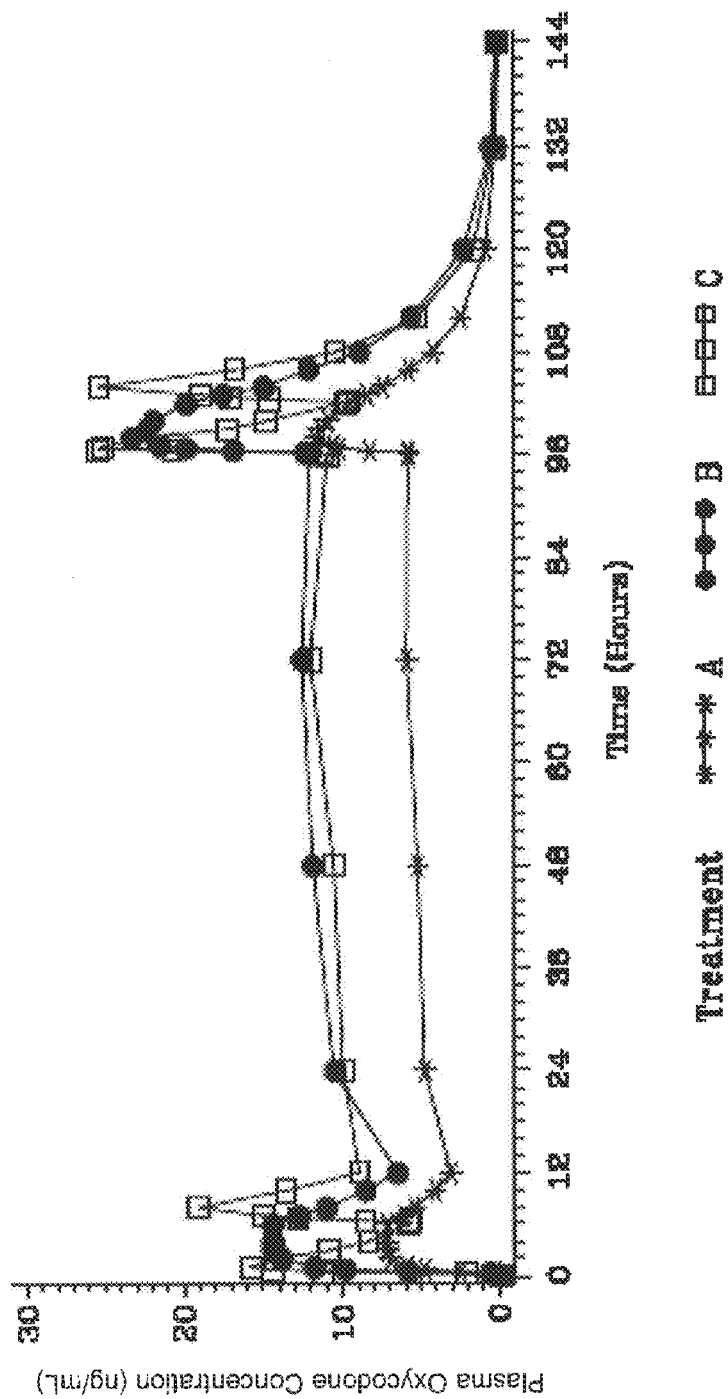


FIG. 25

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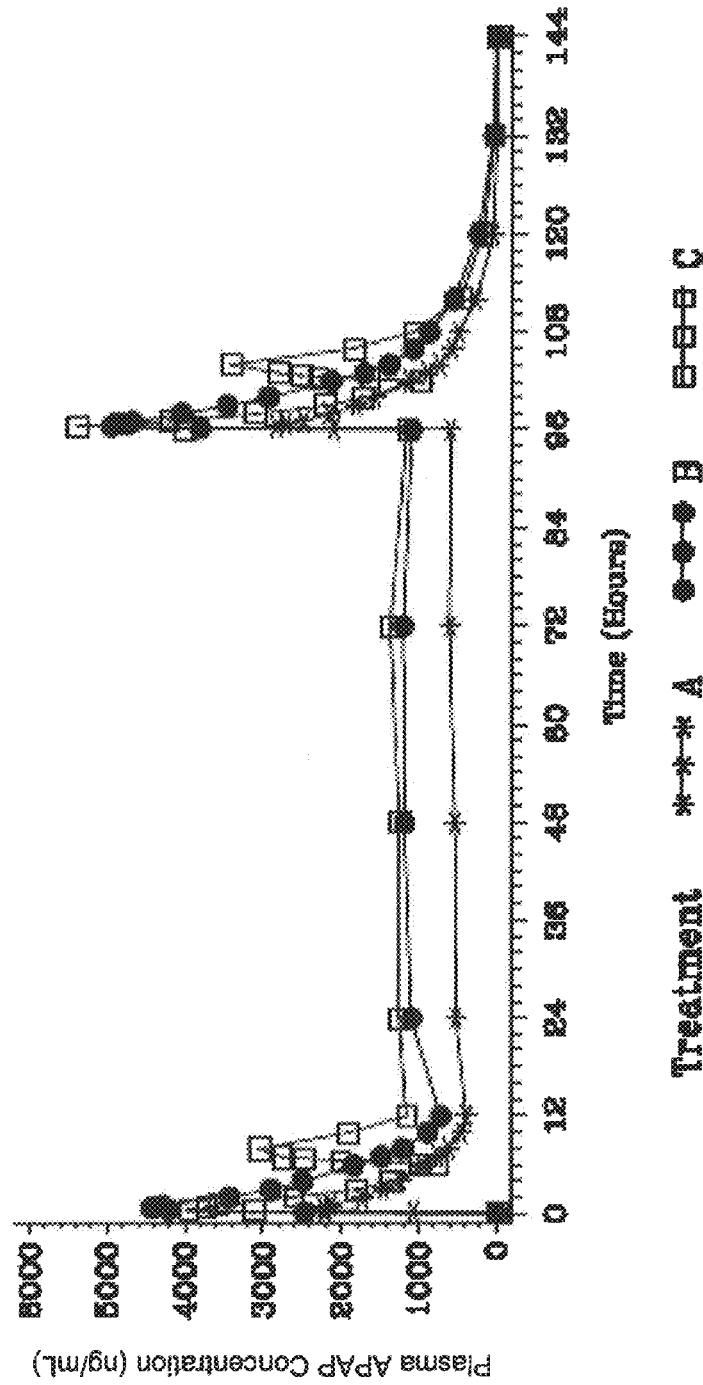


FIG. 26

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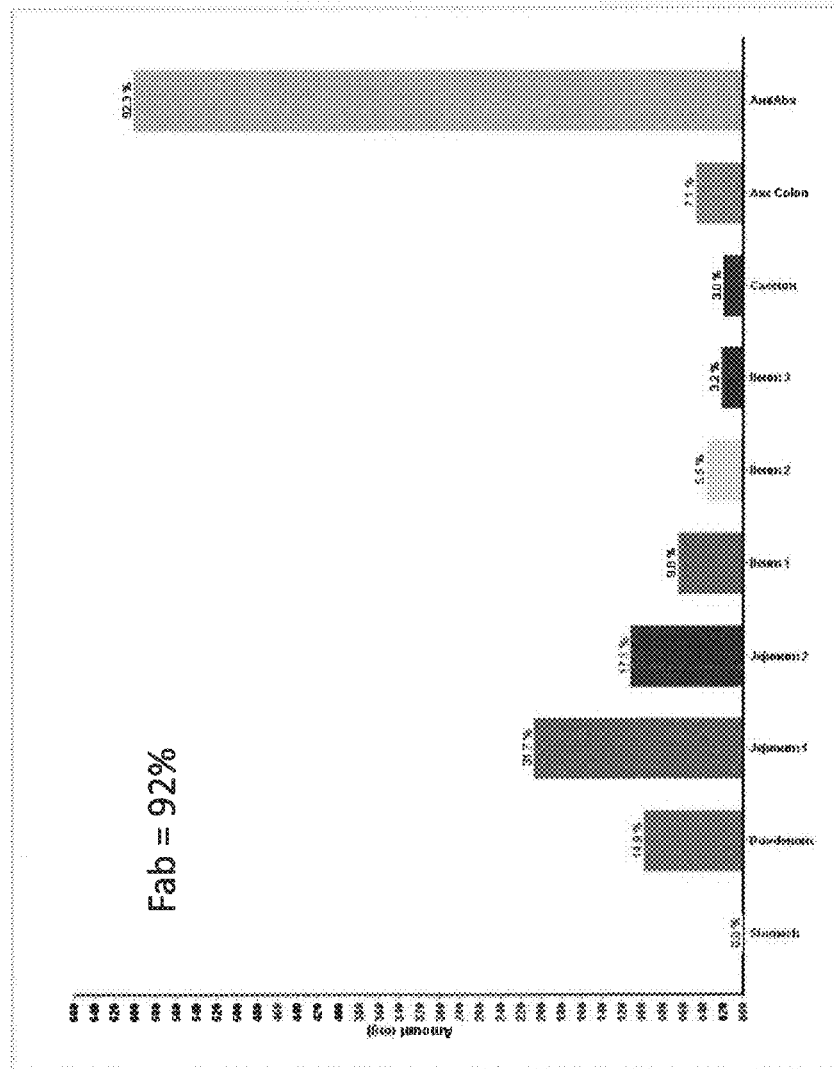


FIG. 27A

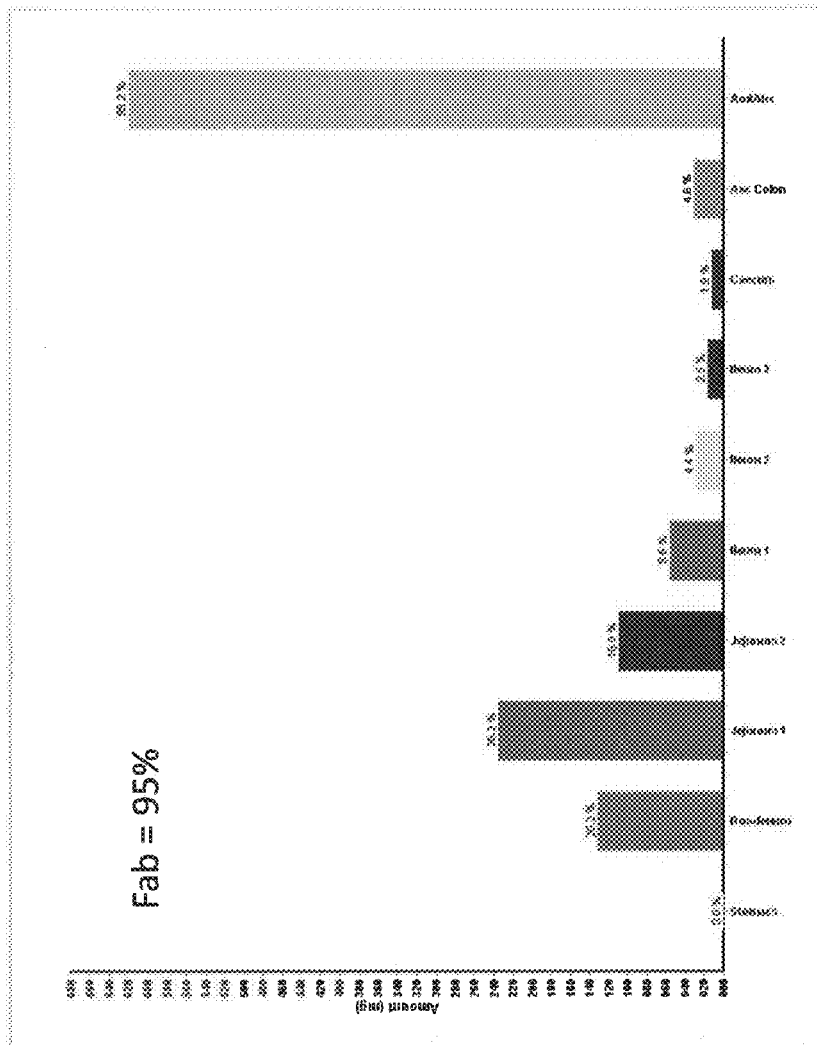


FIG. 27B

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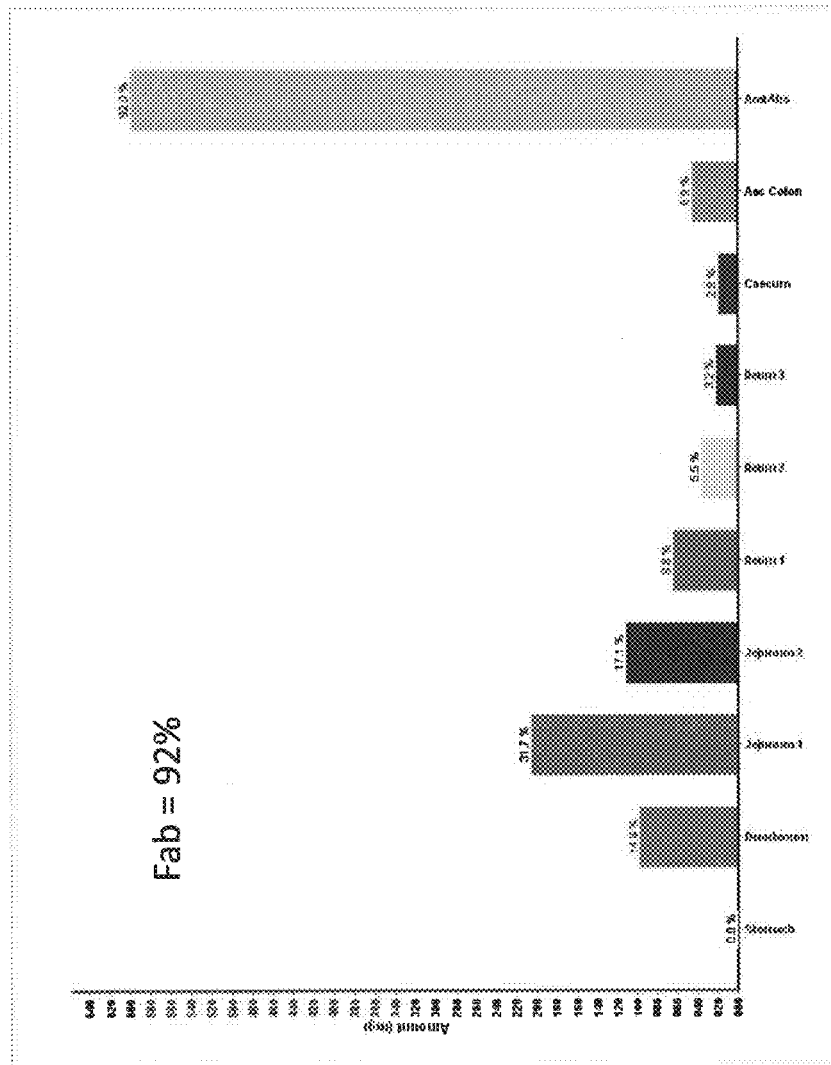
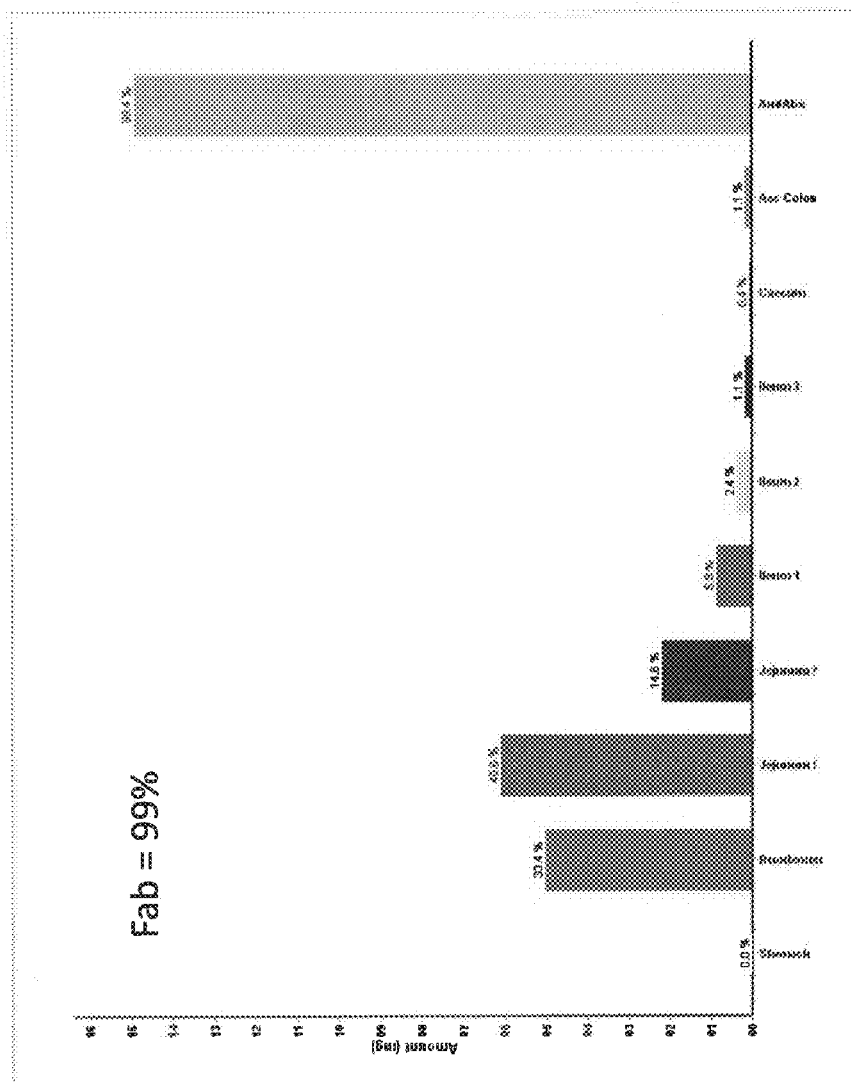


FIG. 27C



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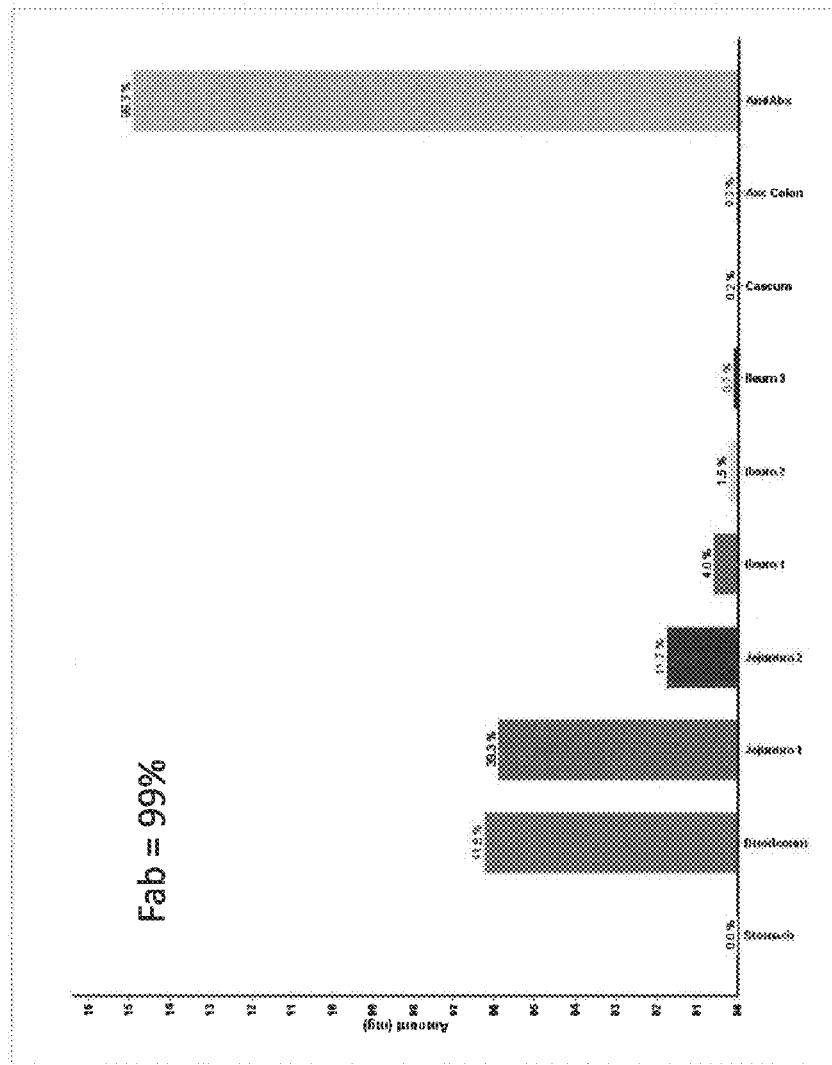


FIG. 28B

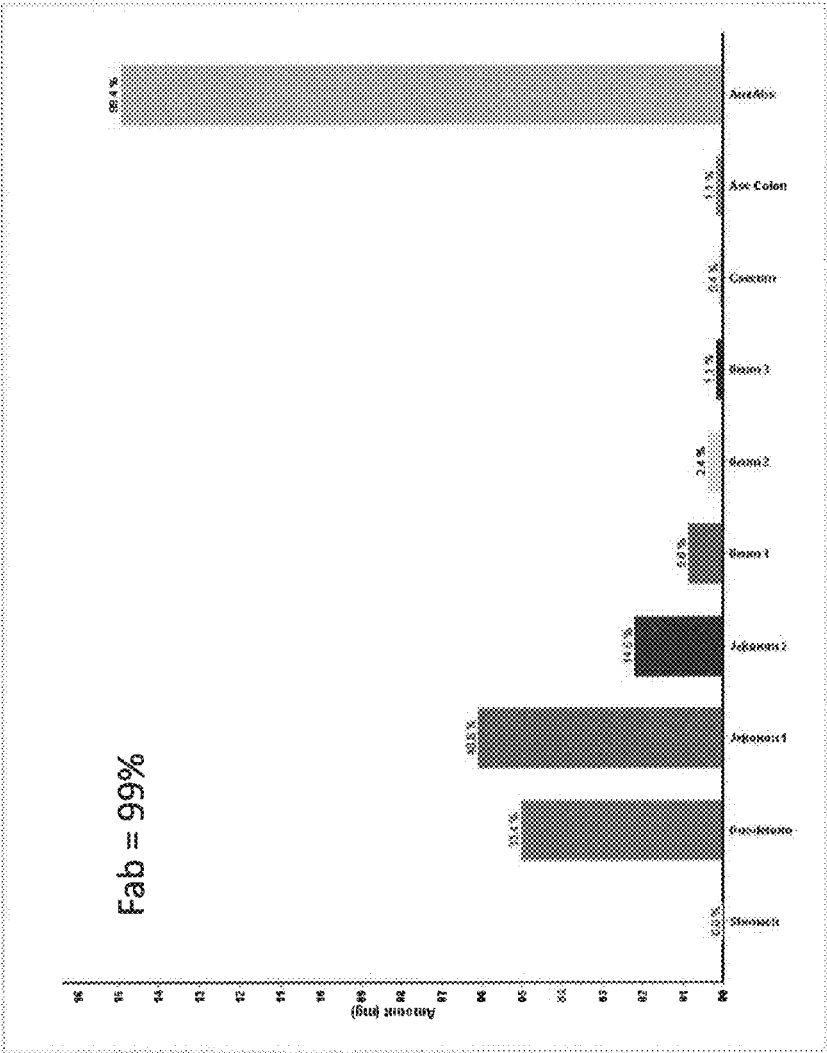


FIG. 28C

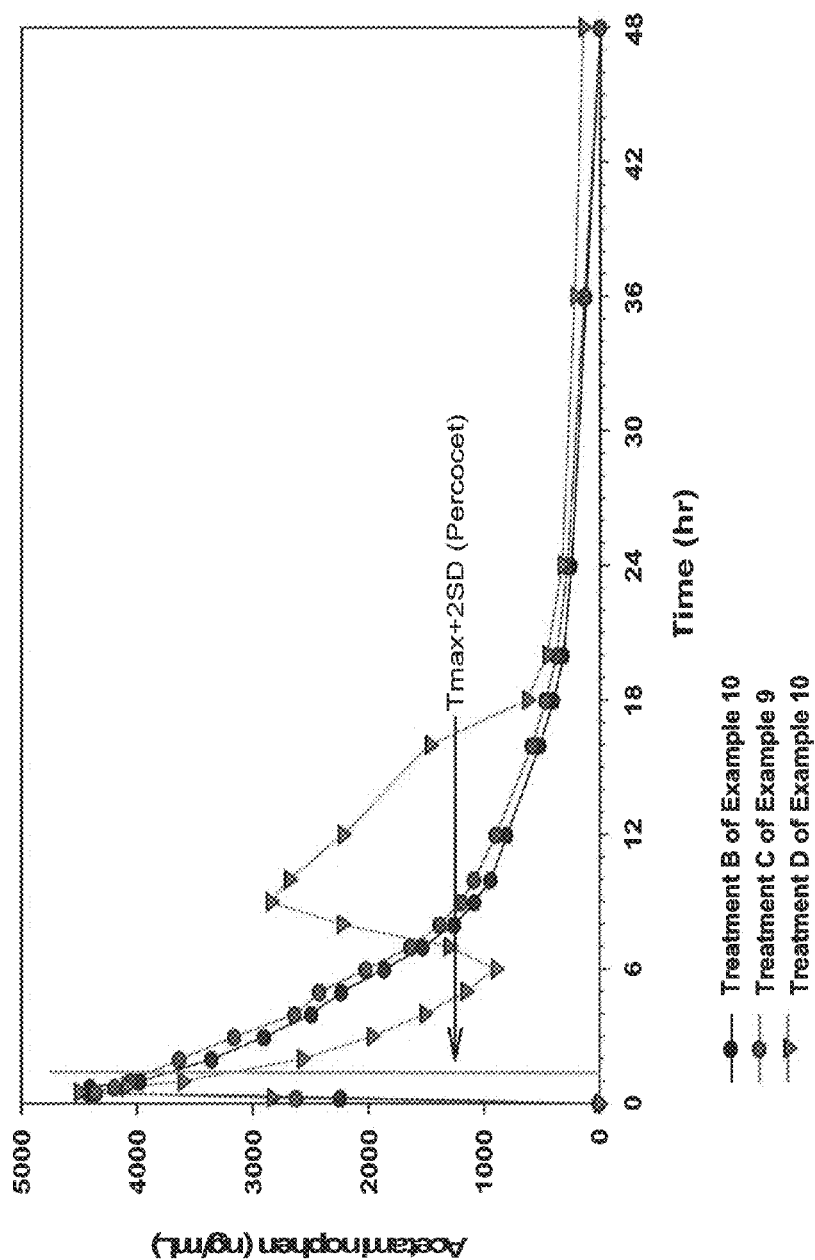


FIG. 29A

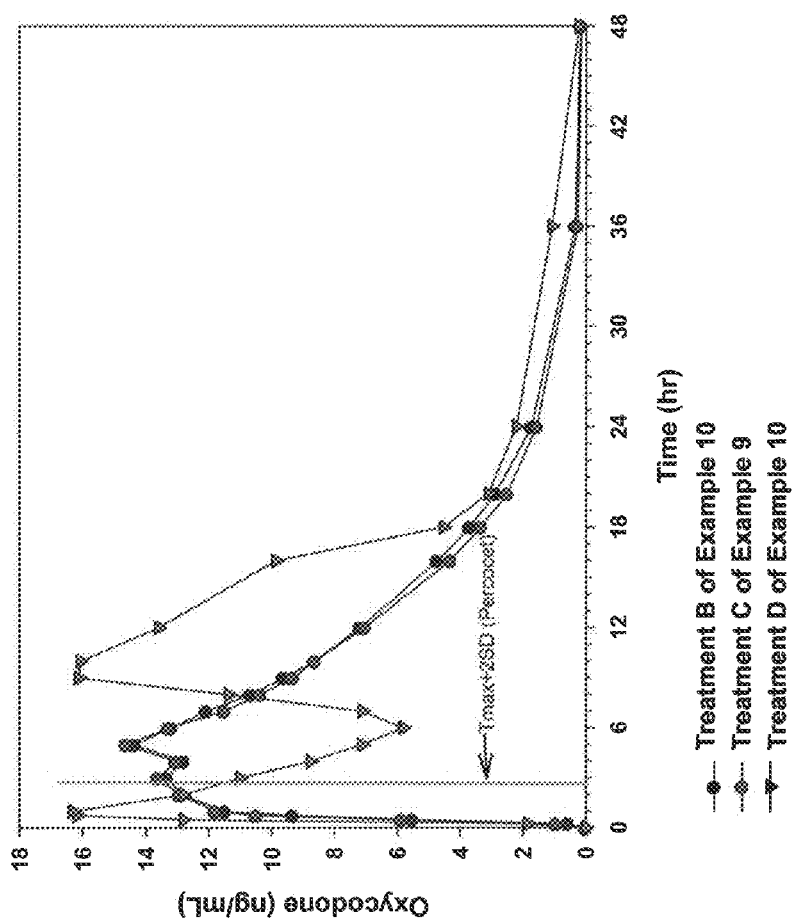


FIG. 29B

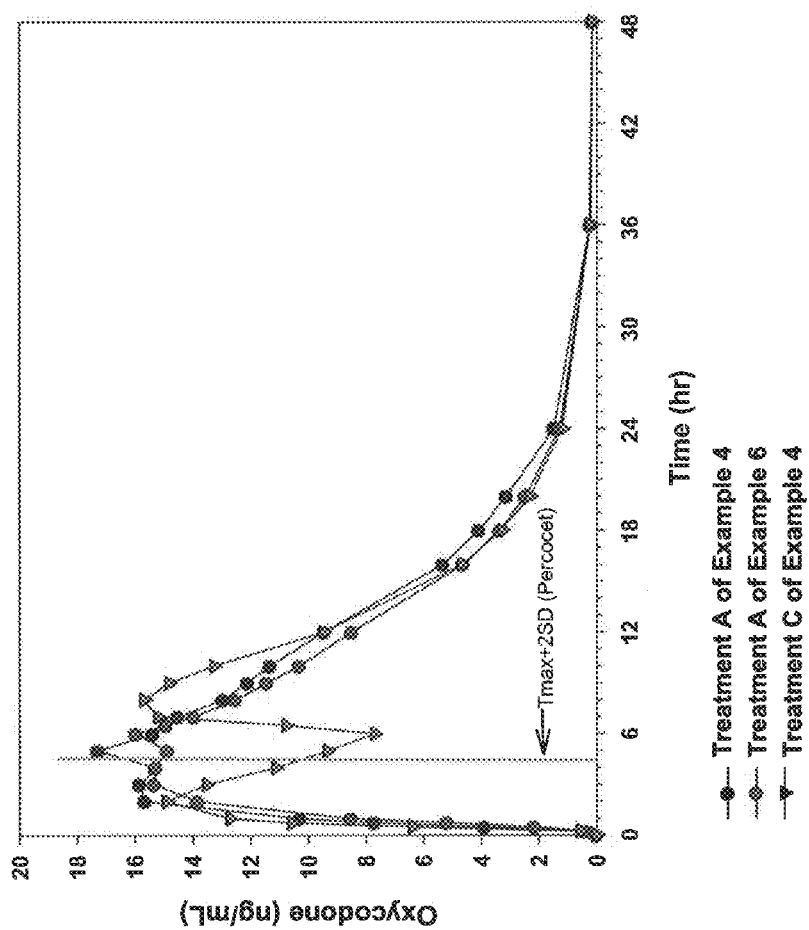


FIG. 30A

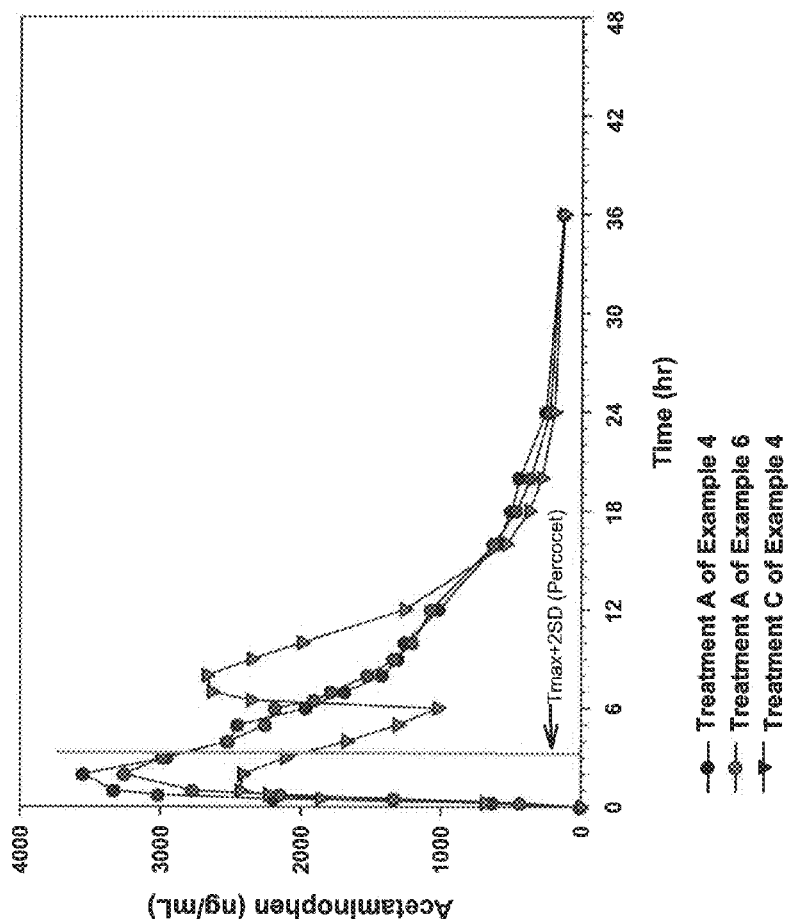


FIG. 30B

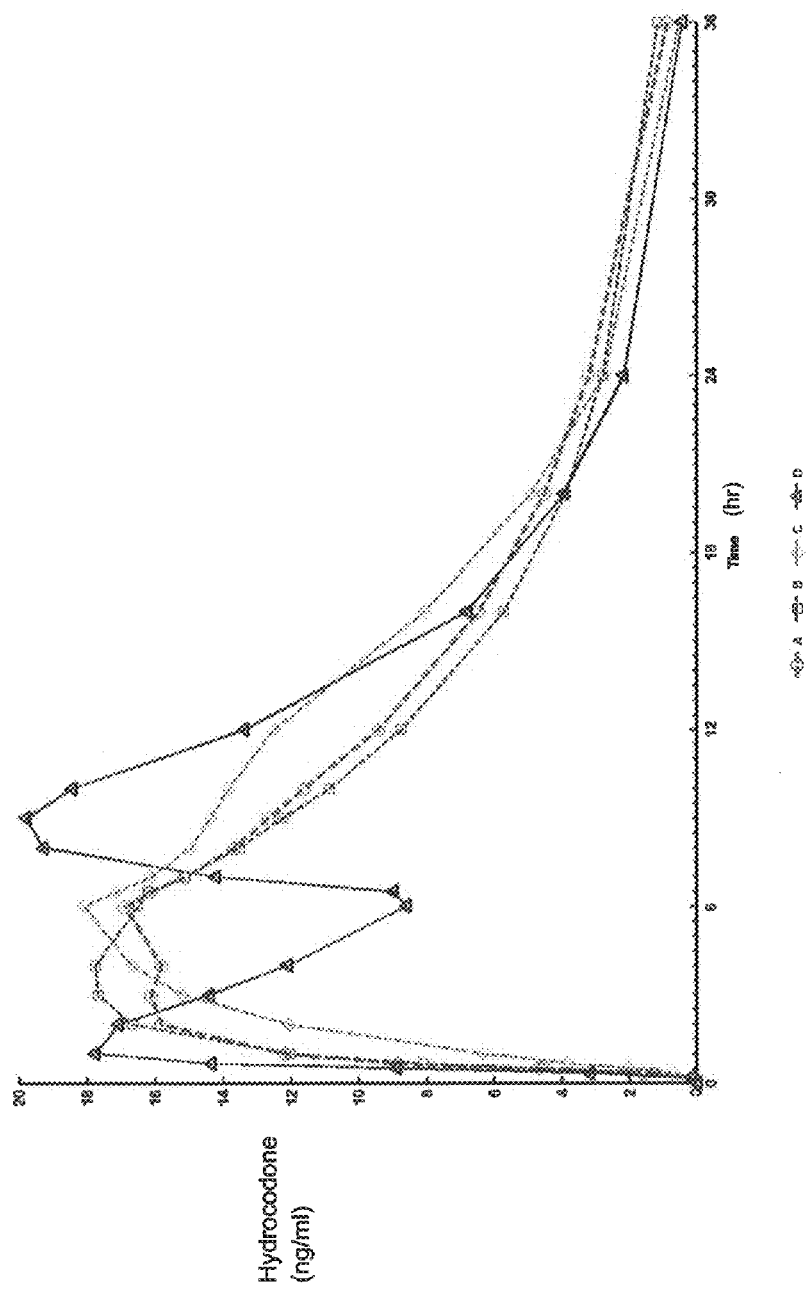


FIG. 31

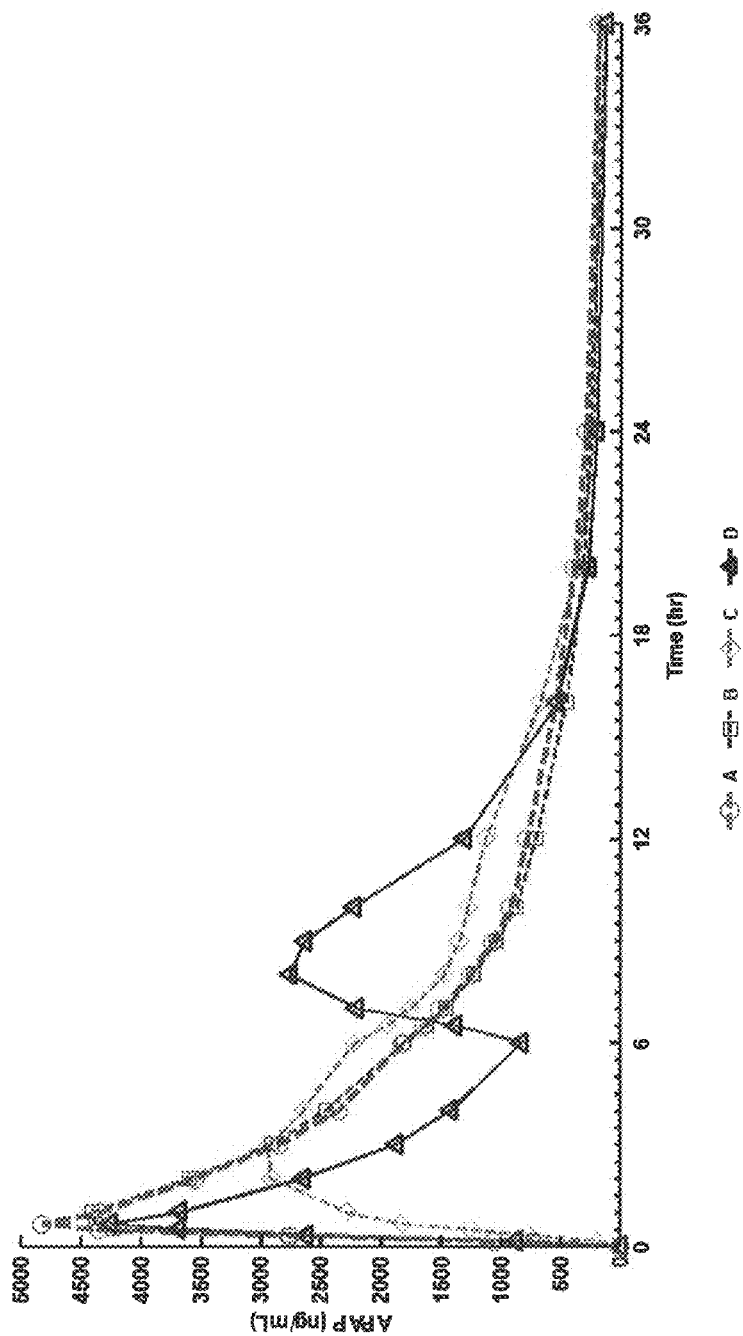


FIG. 32

Mean vs Time ---○--- A ---□--- B ---△--- C ---◇--- D

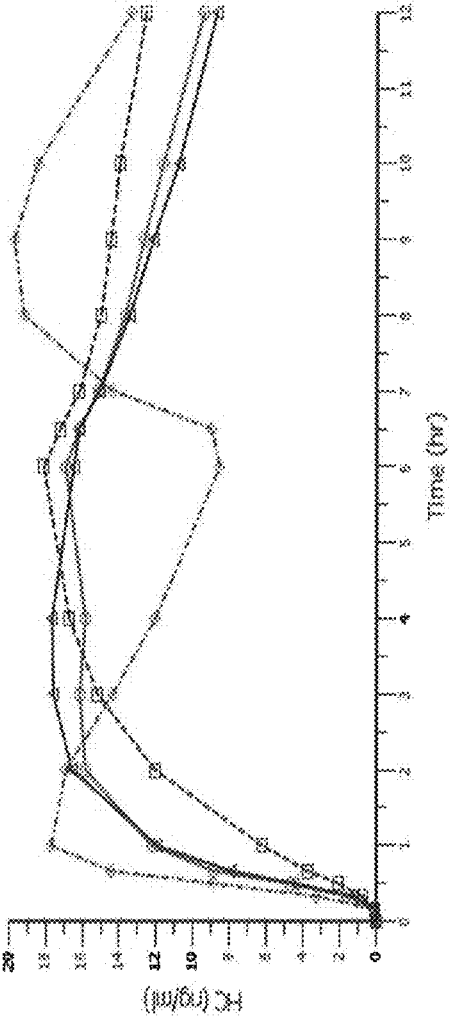


FIG. 33

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Mean vs Time A B C D

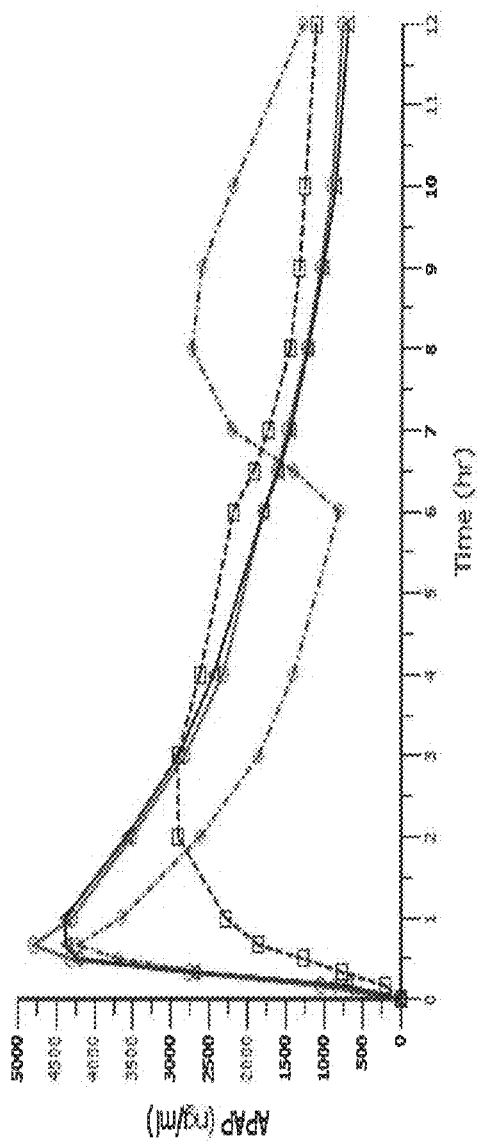


FIG. 34

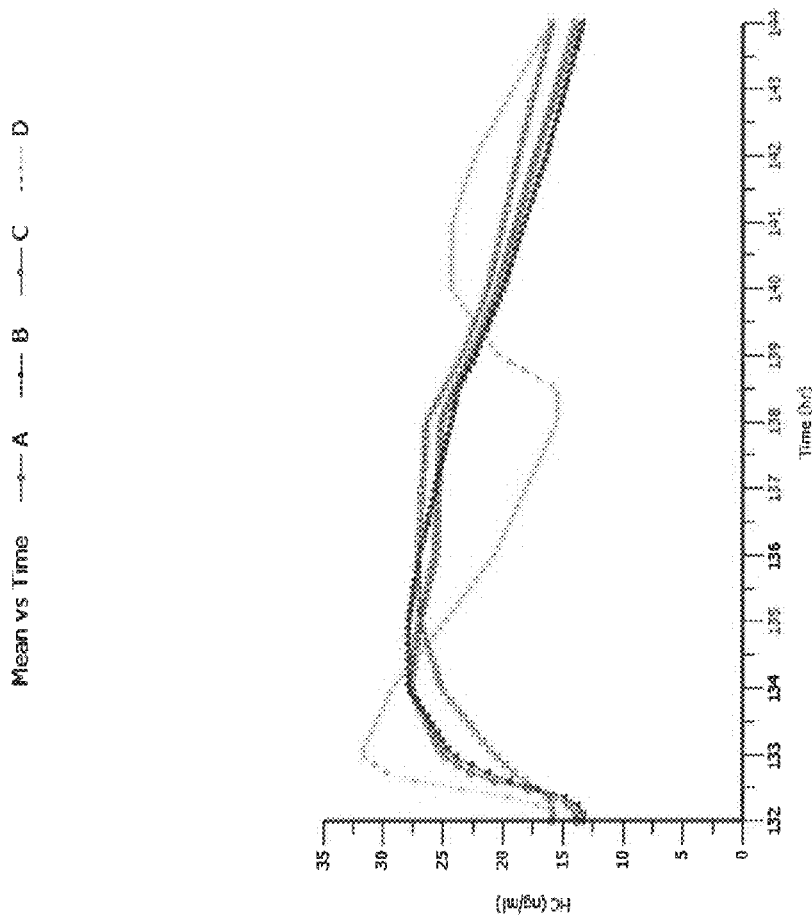


FIG. 35

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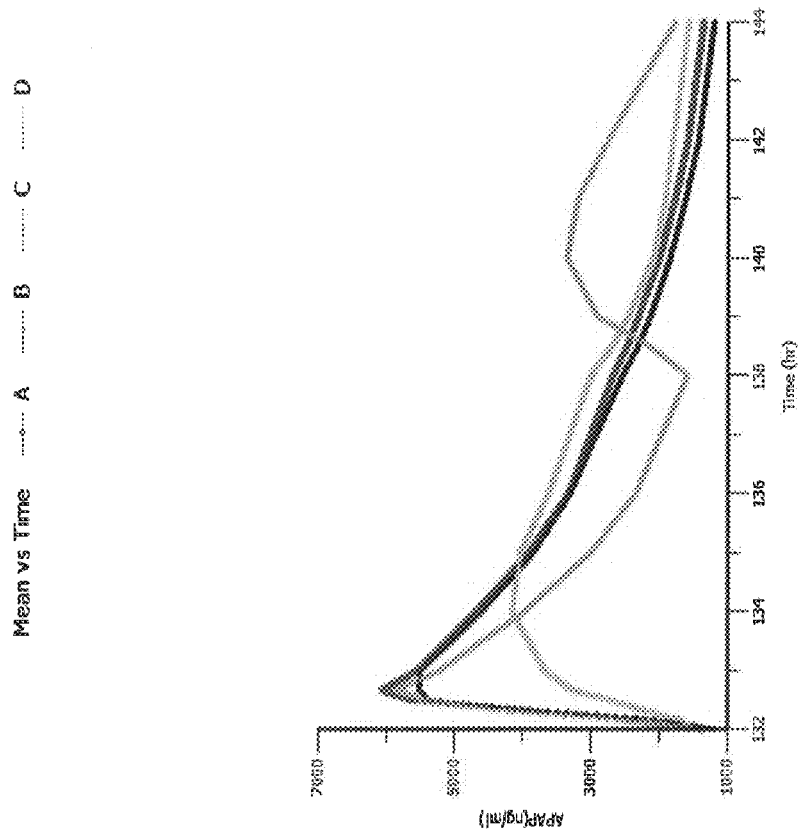


FIG. 36

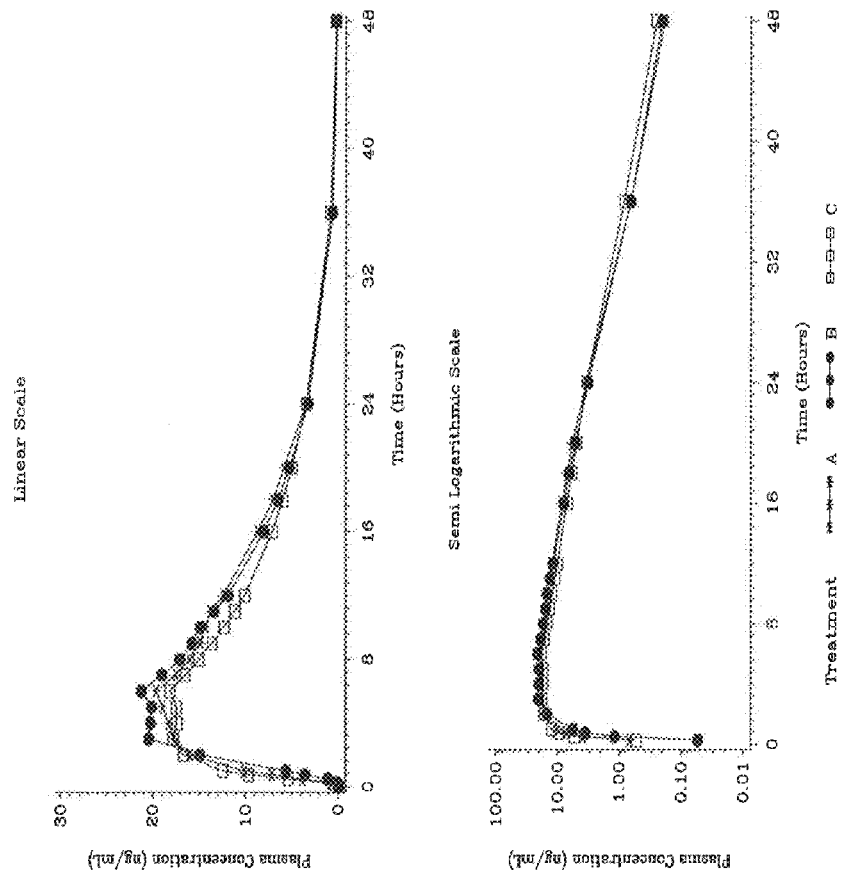


FIG. 37

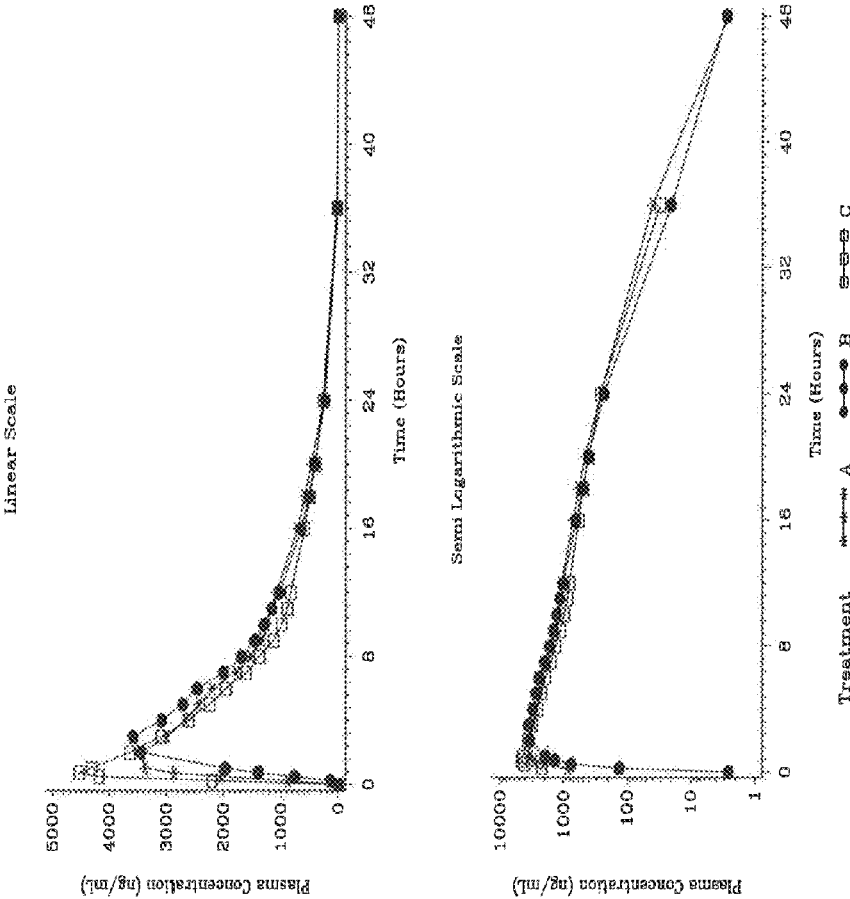


FIG. 38

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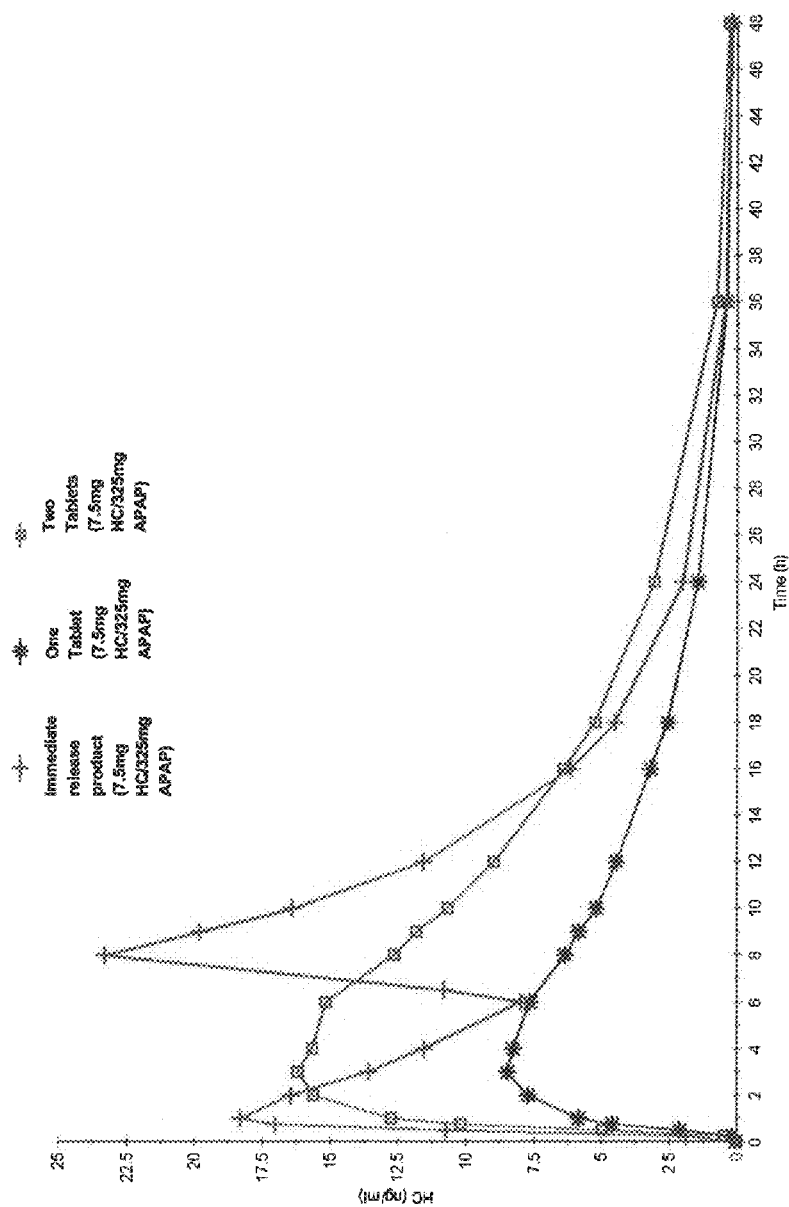


FIG. 39

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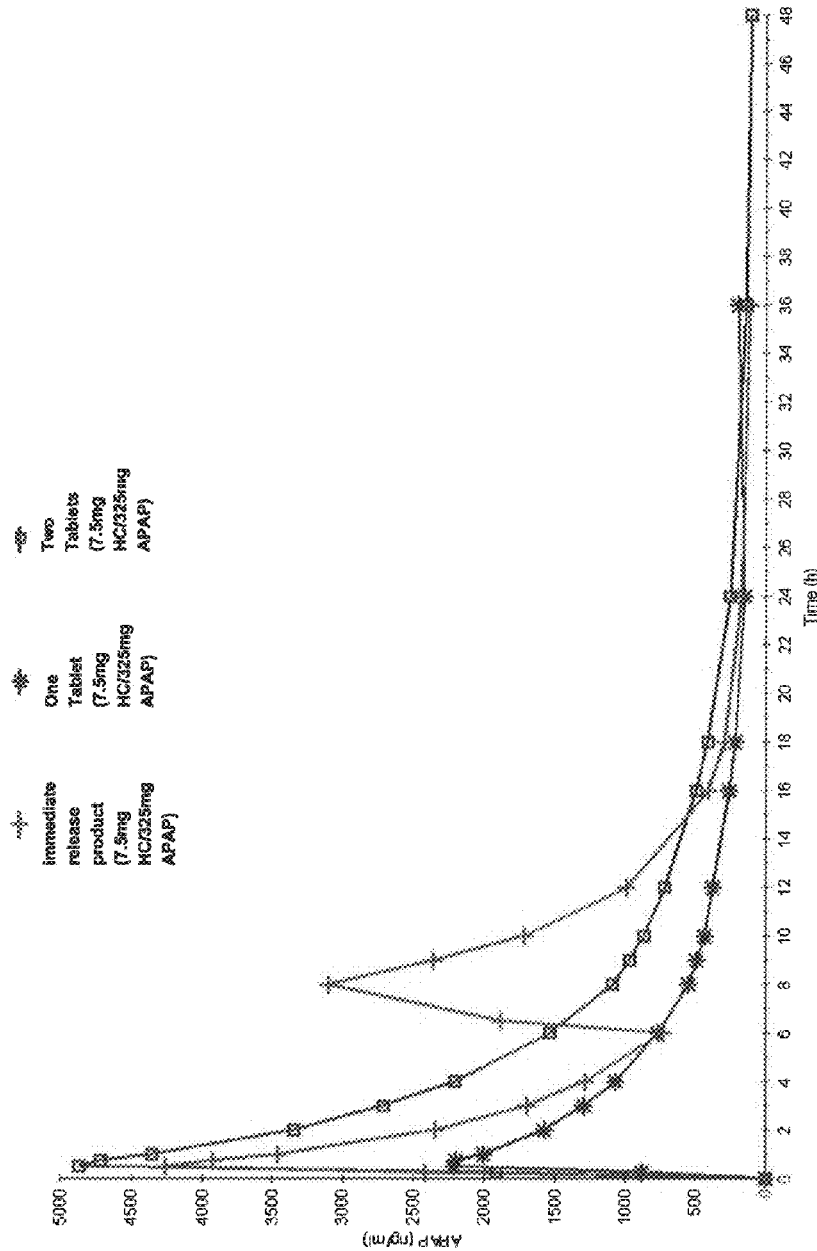


FIG. 40

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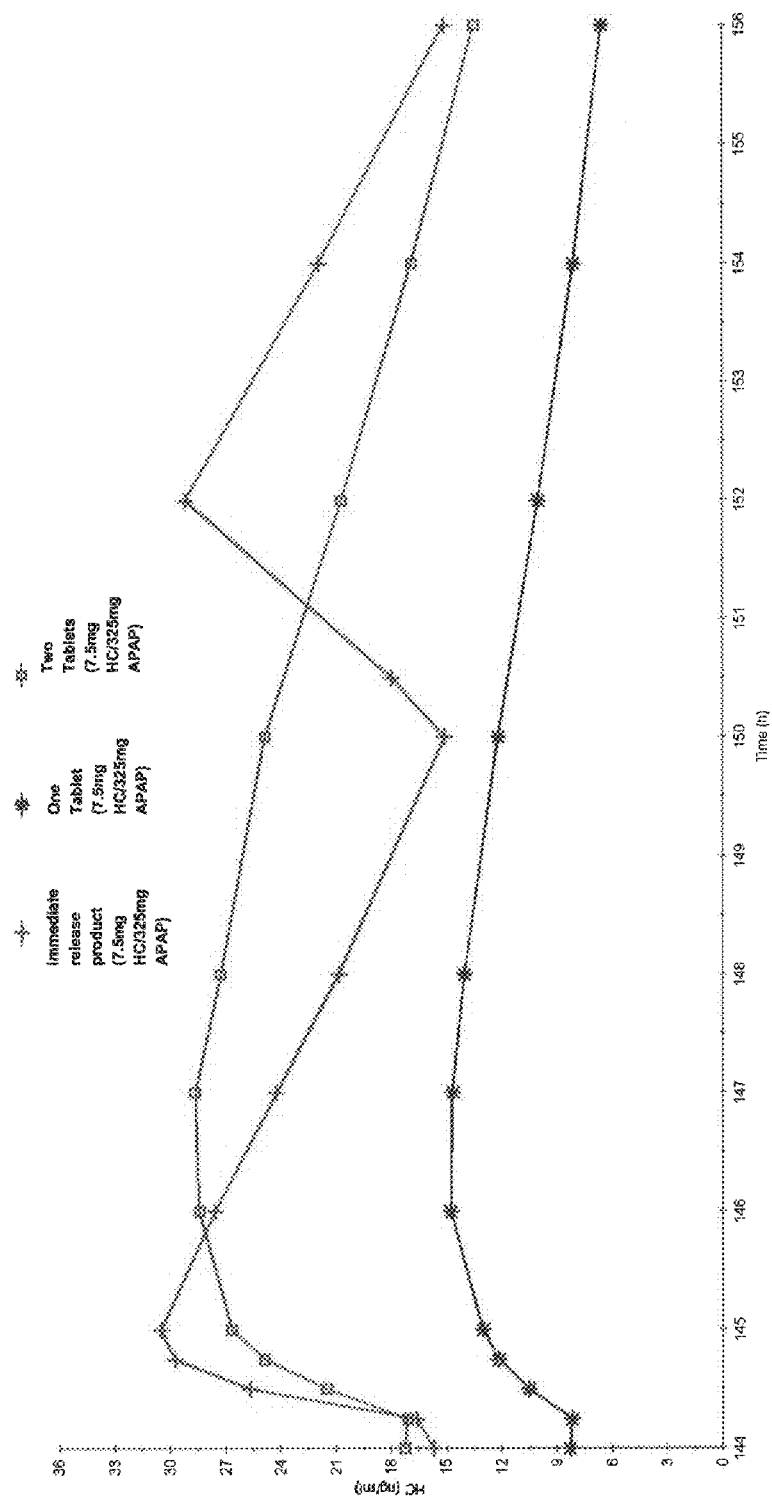


FIG. 41

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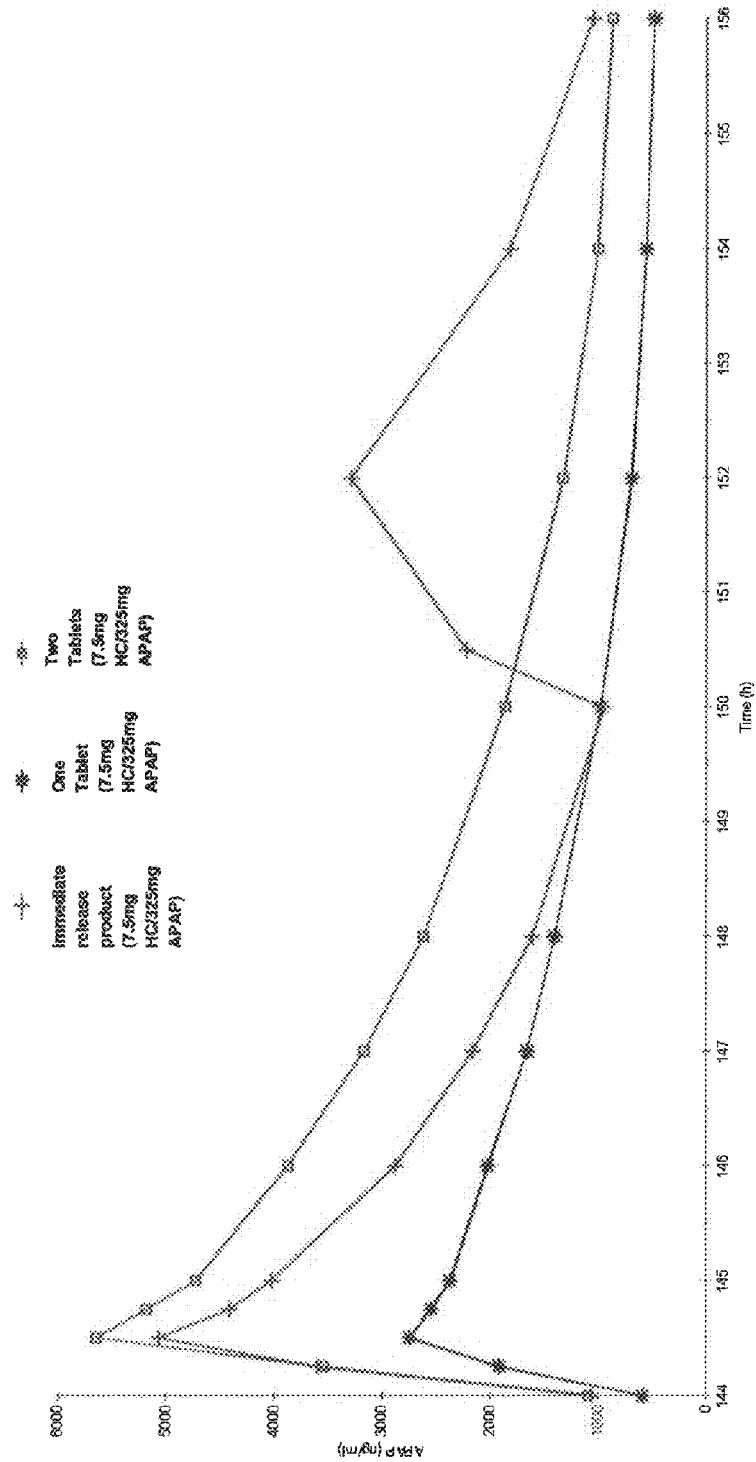


FIG. 42

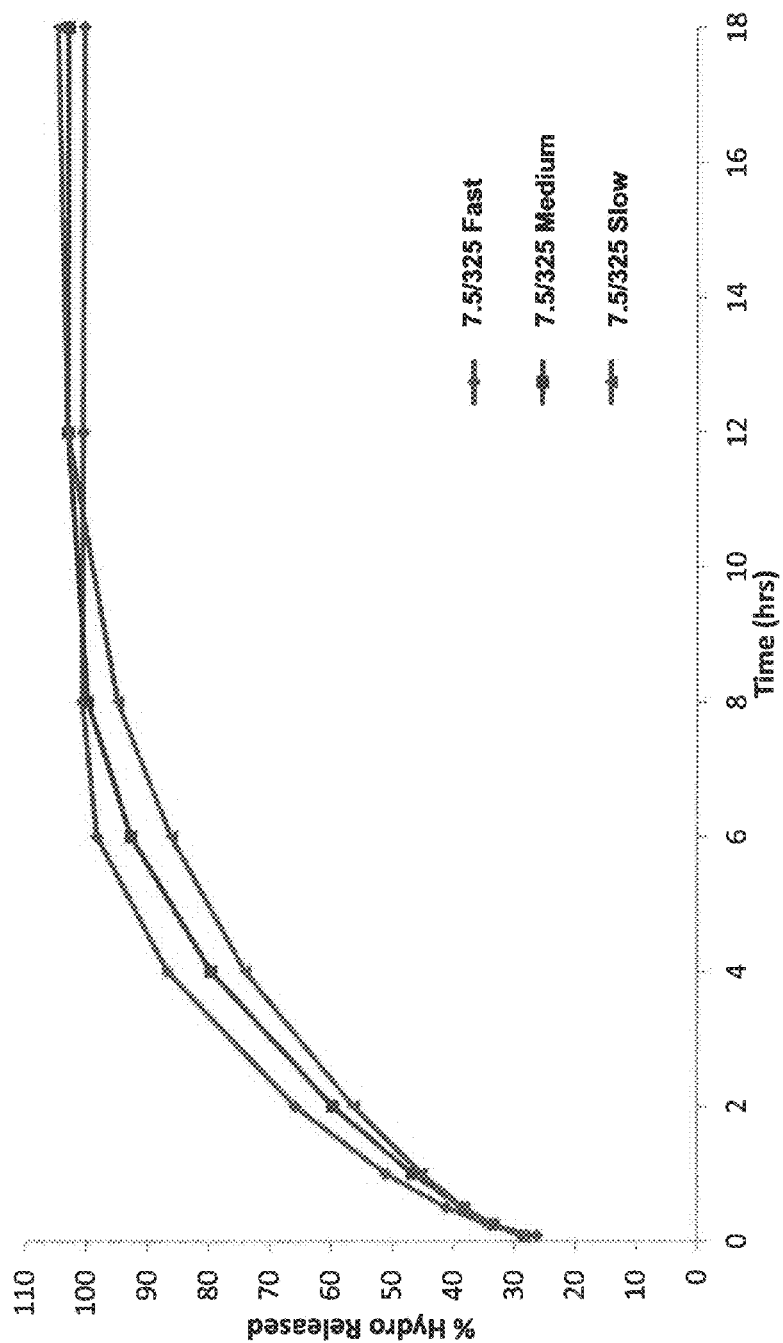


FIG. 43

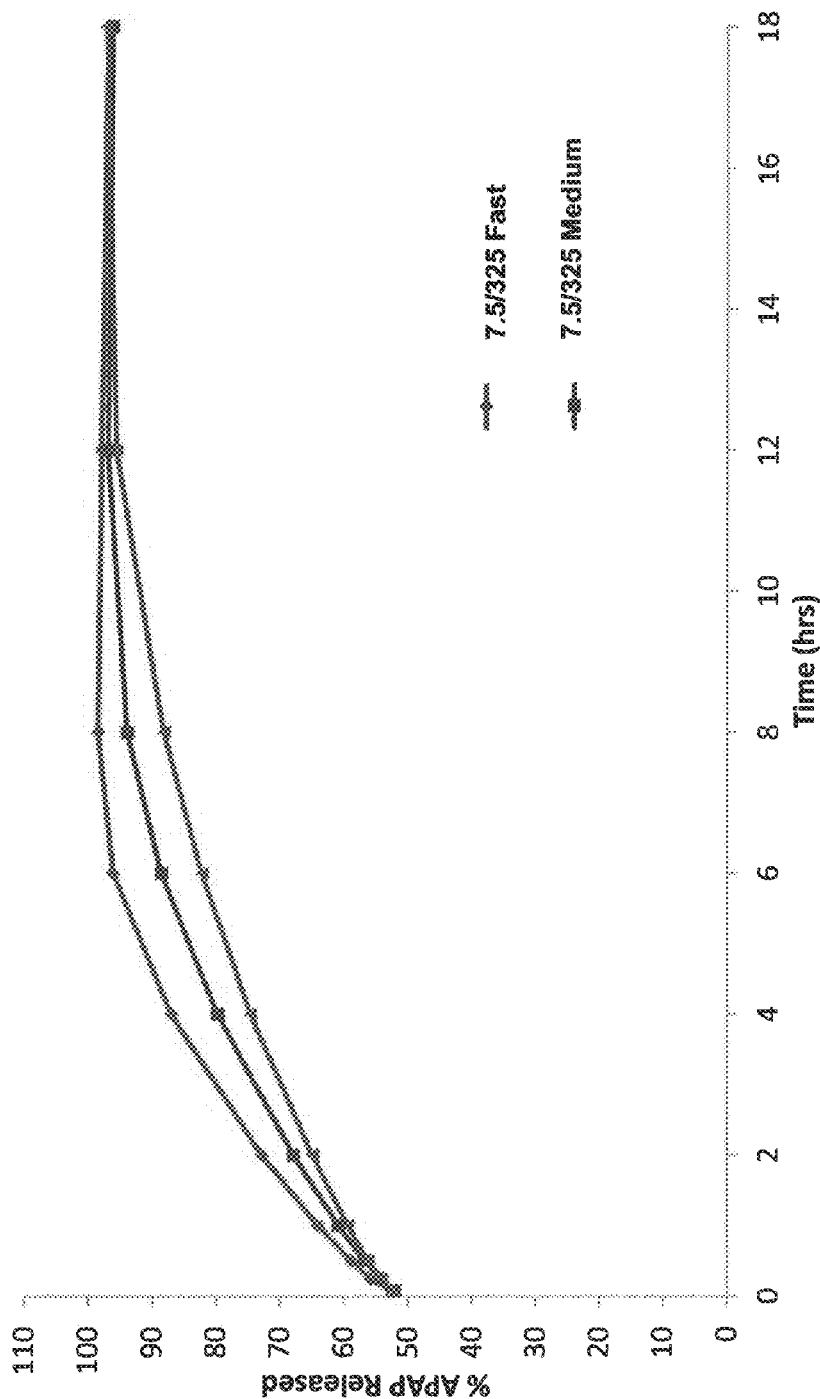


FIG. 44

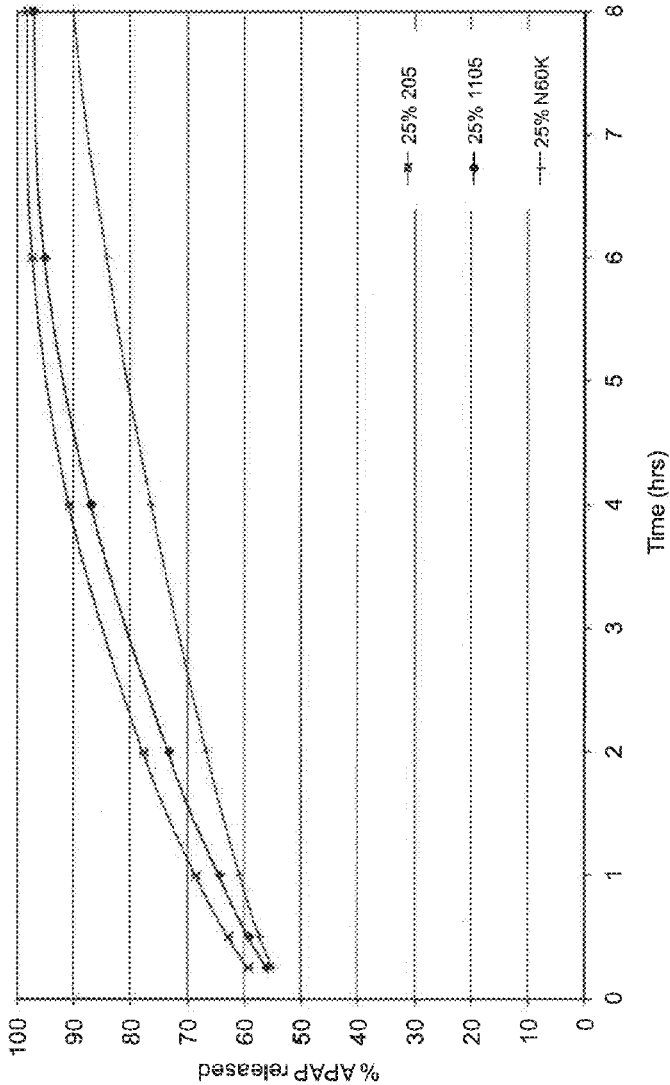


FIG. 45

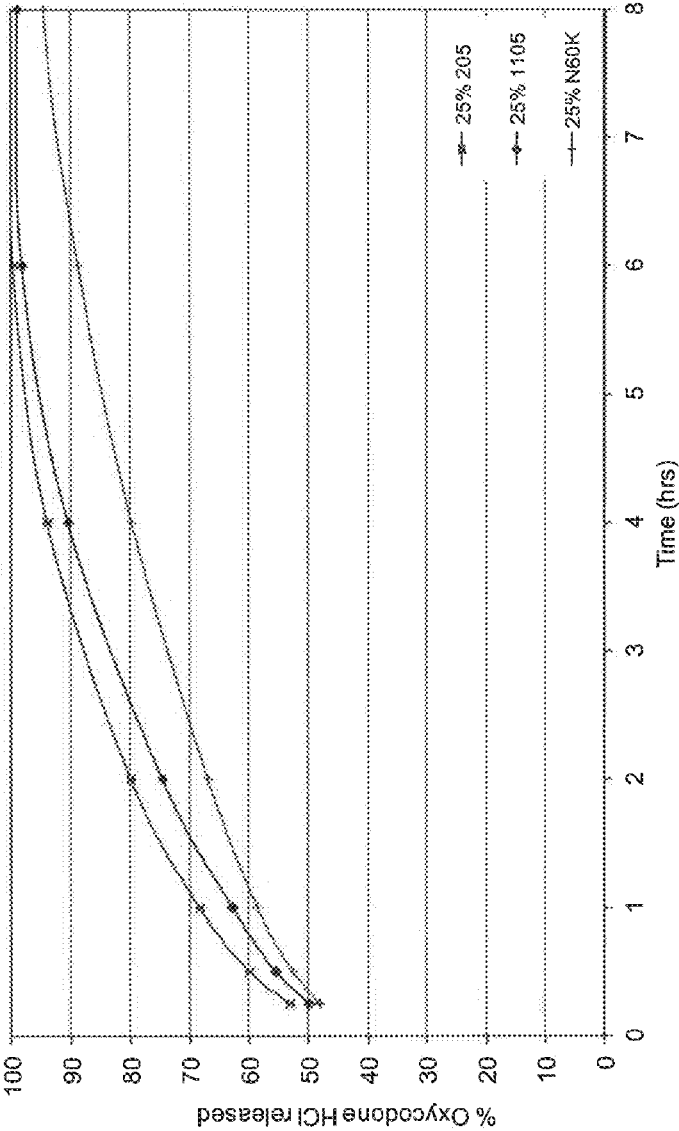


FIG. 46

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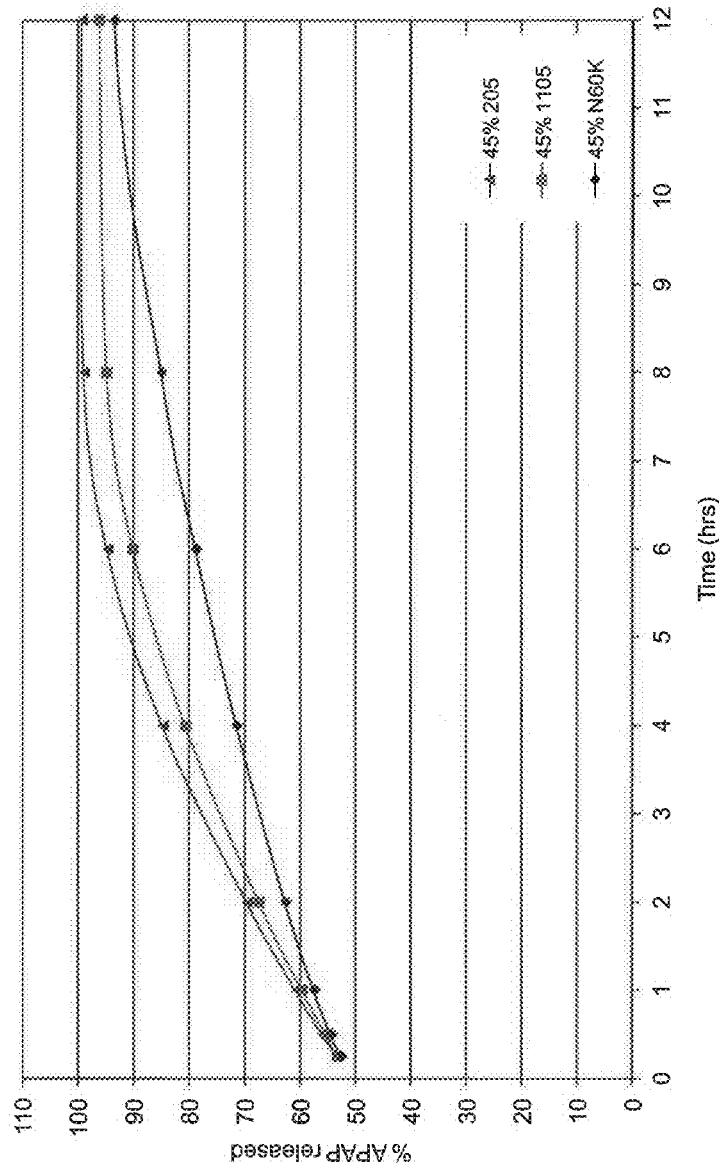


FIG. 47

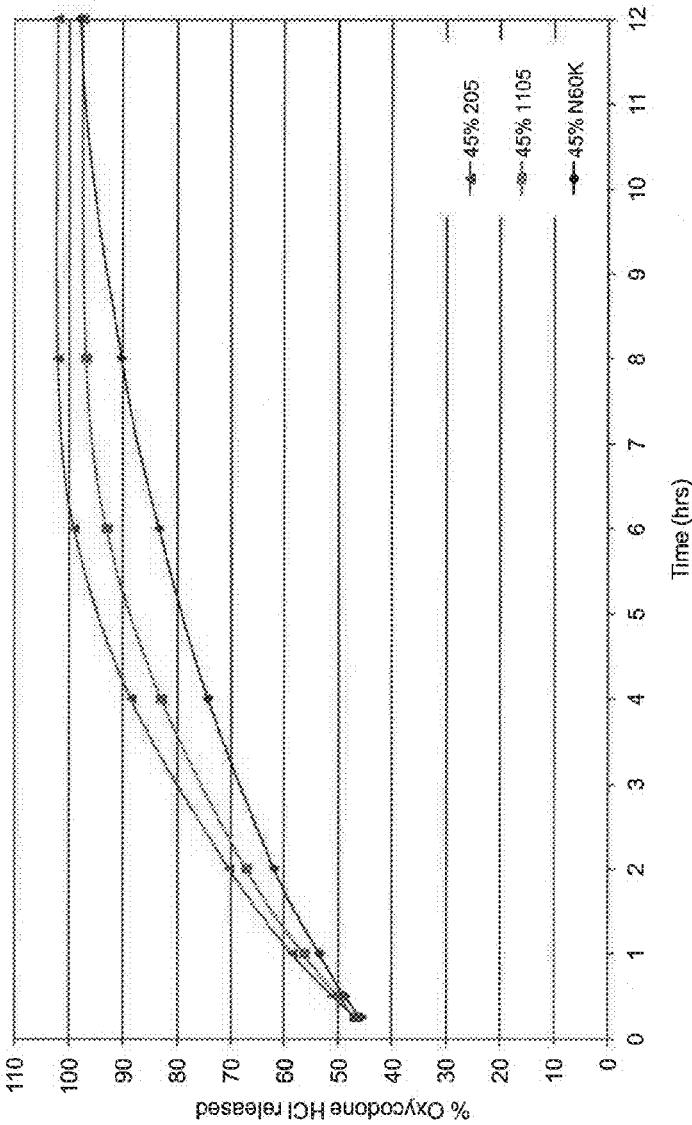


FIG. 48

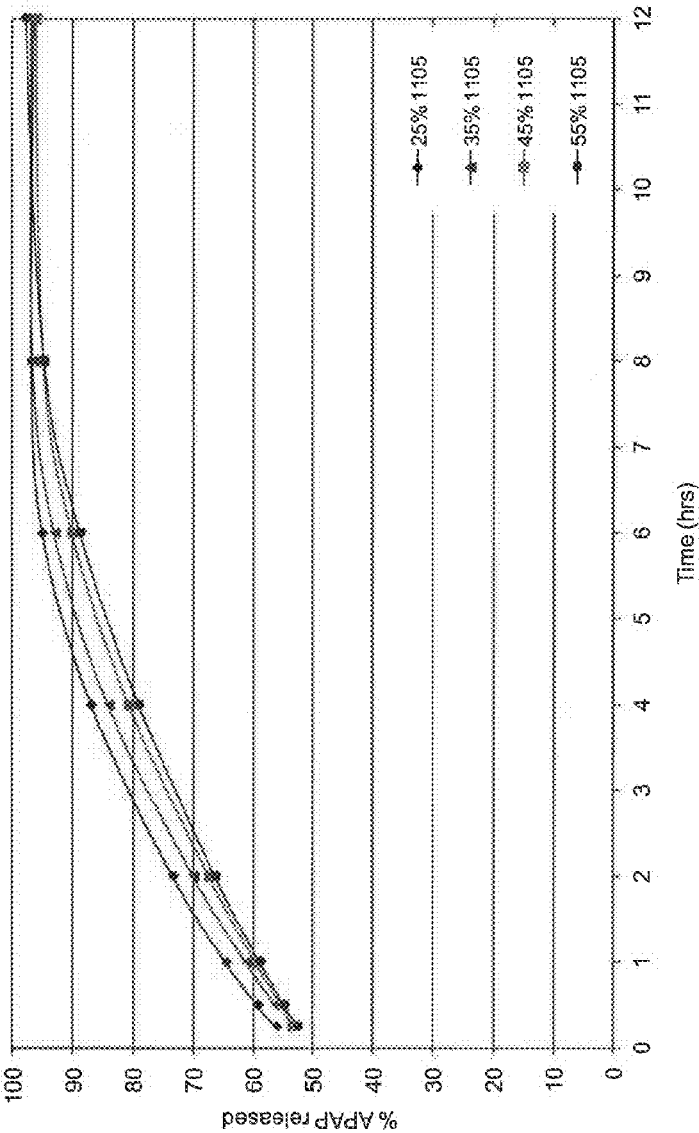


FIG. 49

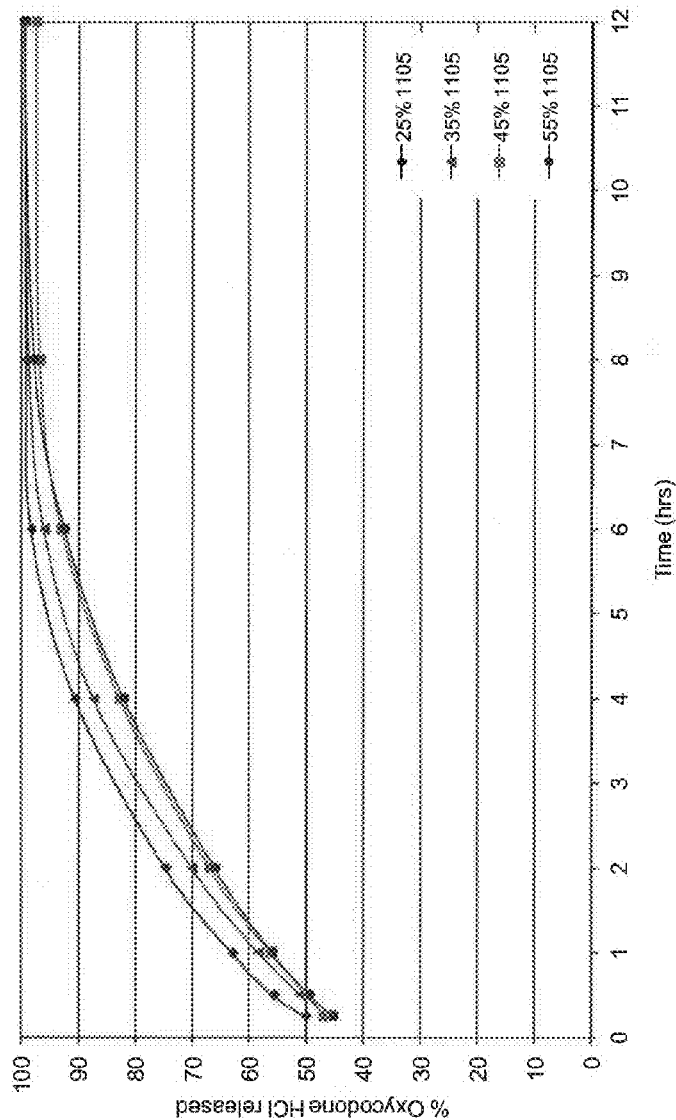


FIG. 50

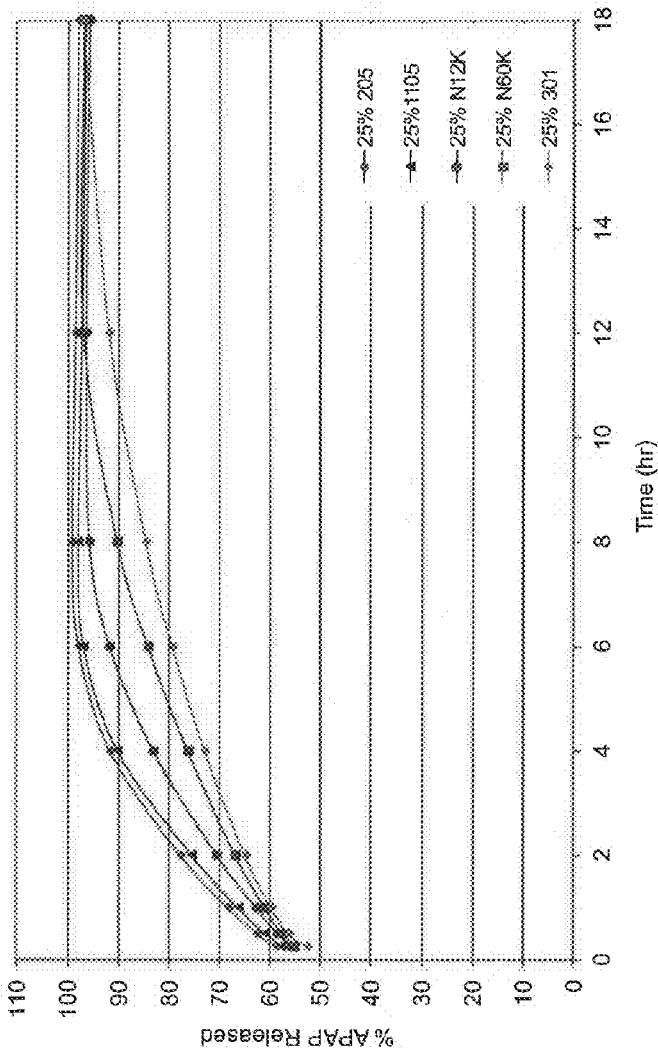


FIG. 51

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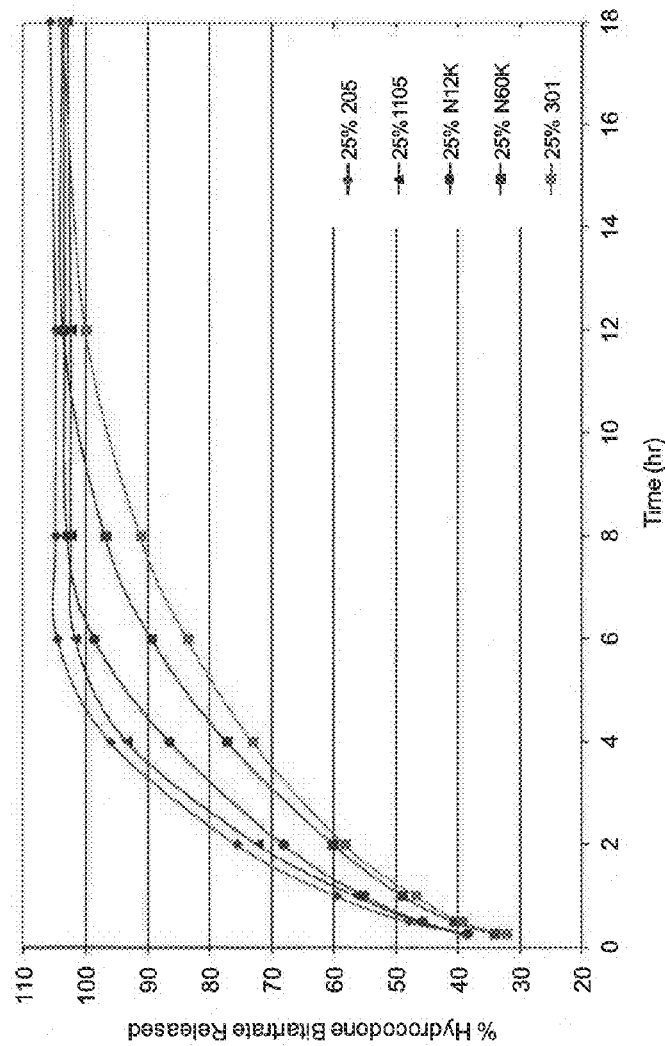


FIG. 52

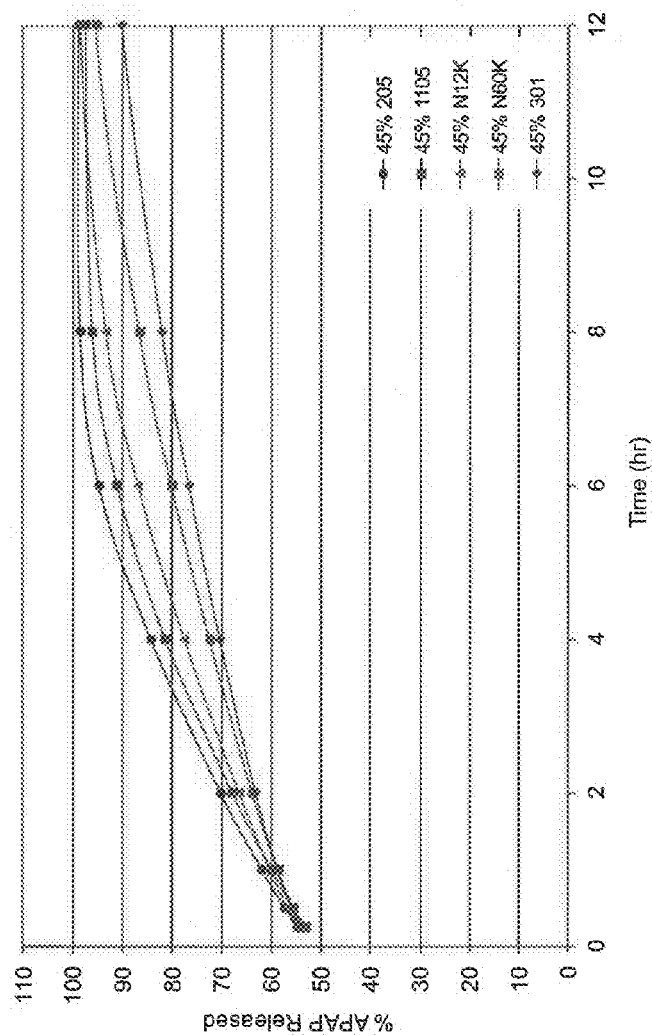


FIG. 53

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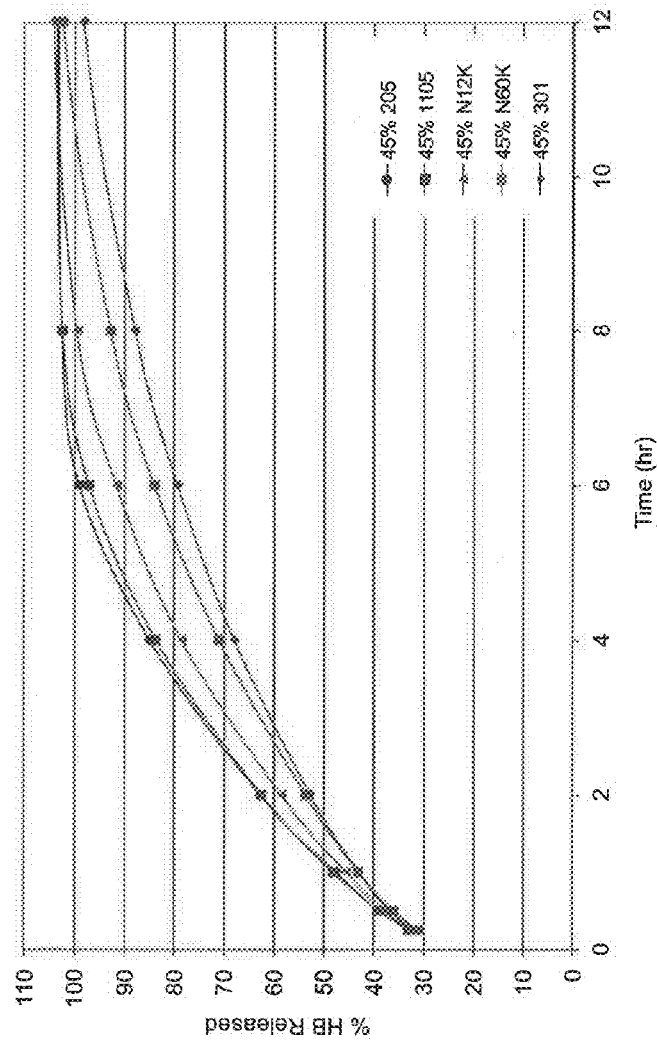


FIG. 54

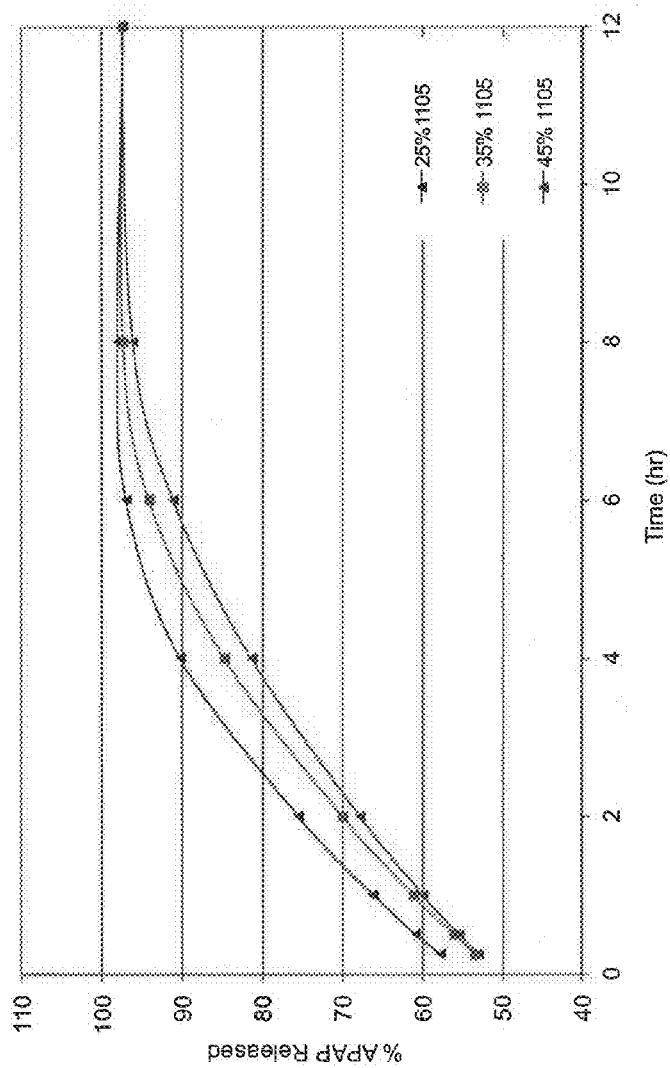


FIG. 55

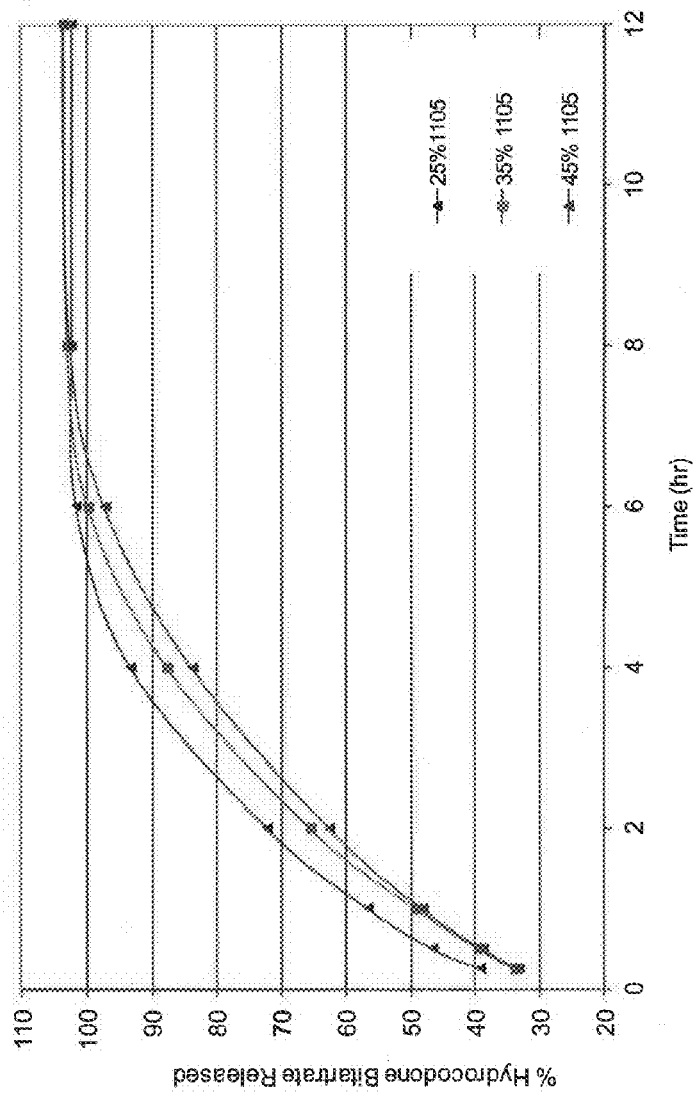


FIG. 56

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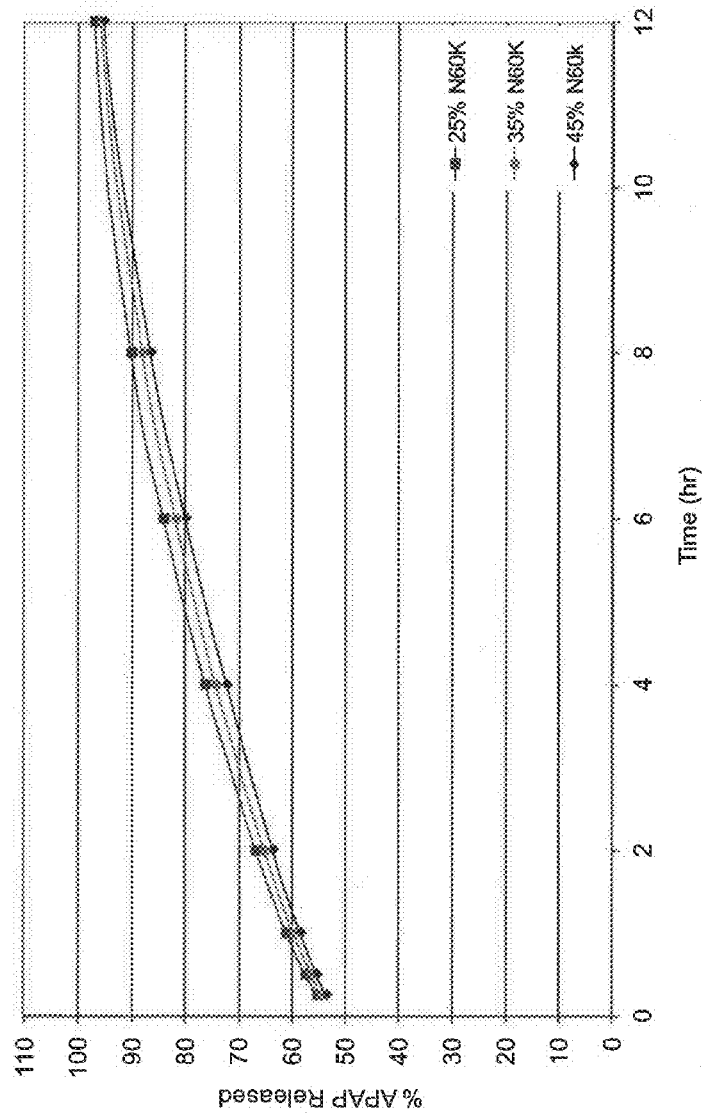


FIG. 57

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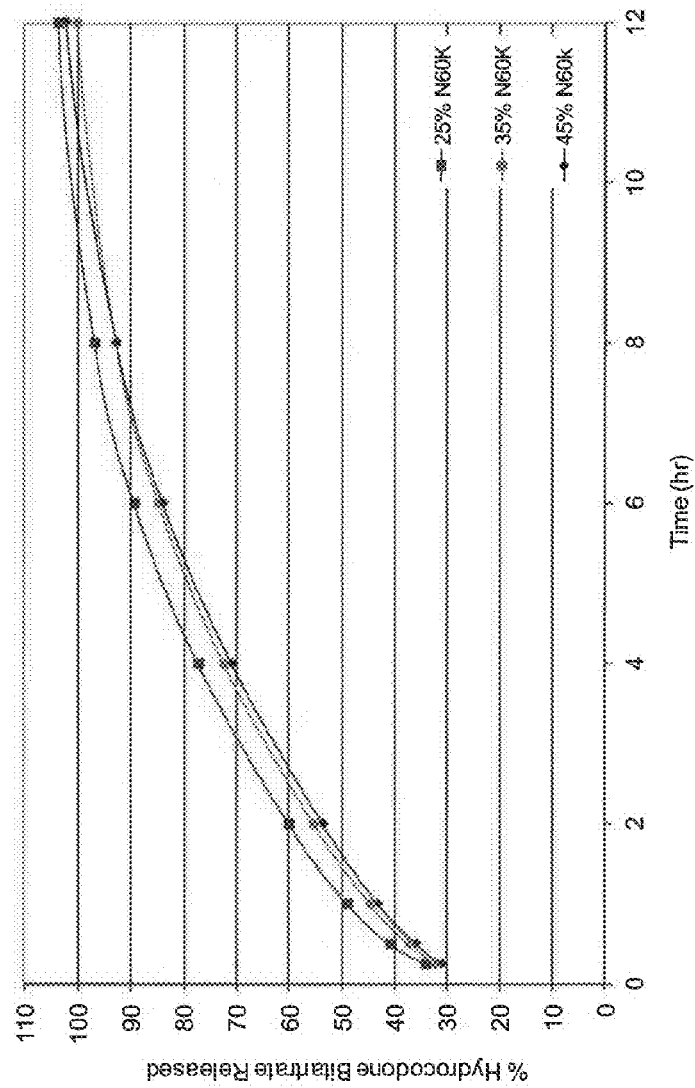


FIG. 58

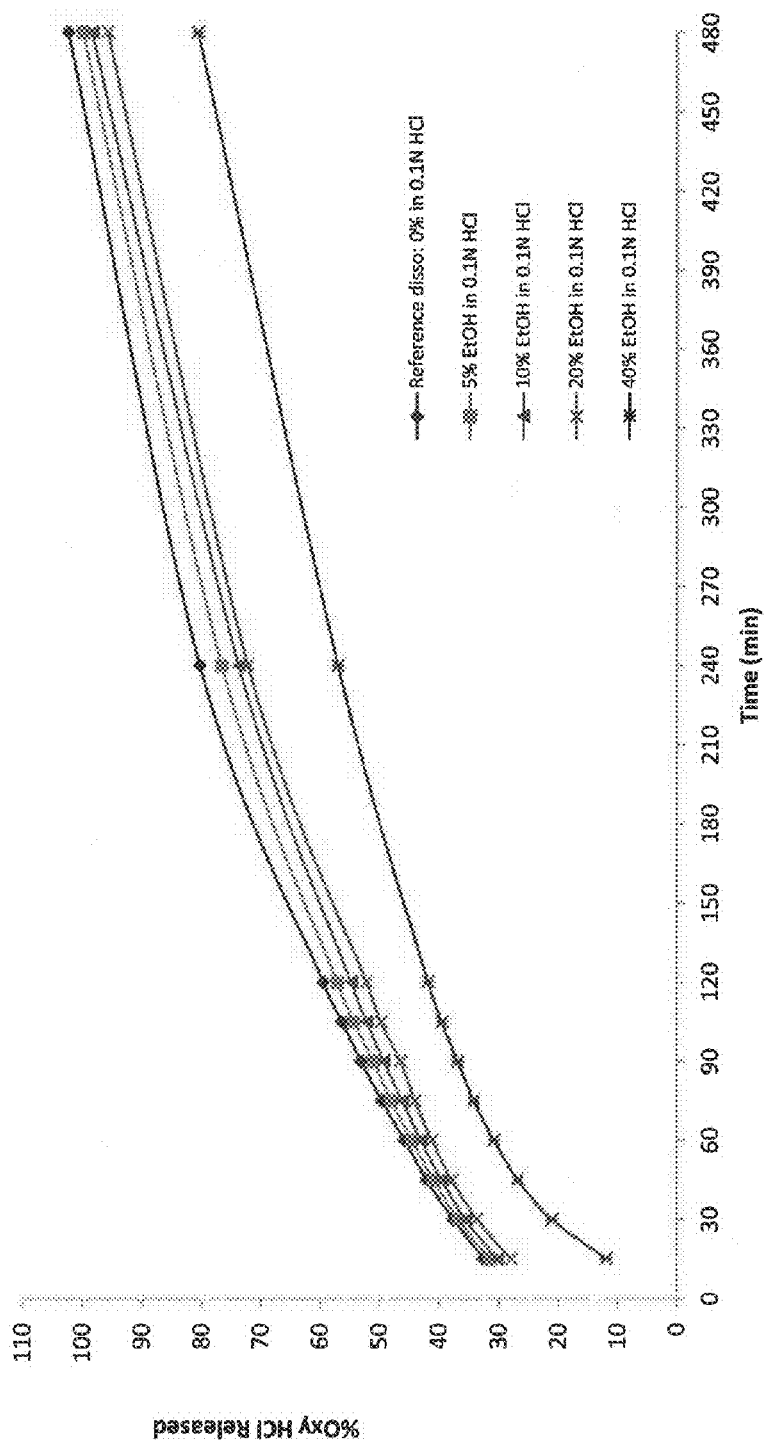


FIG. 59

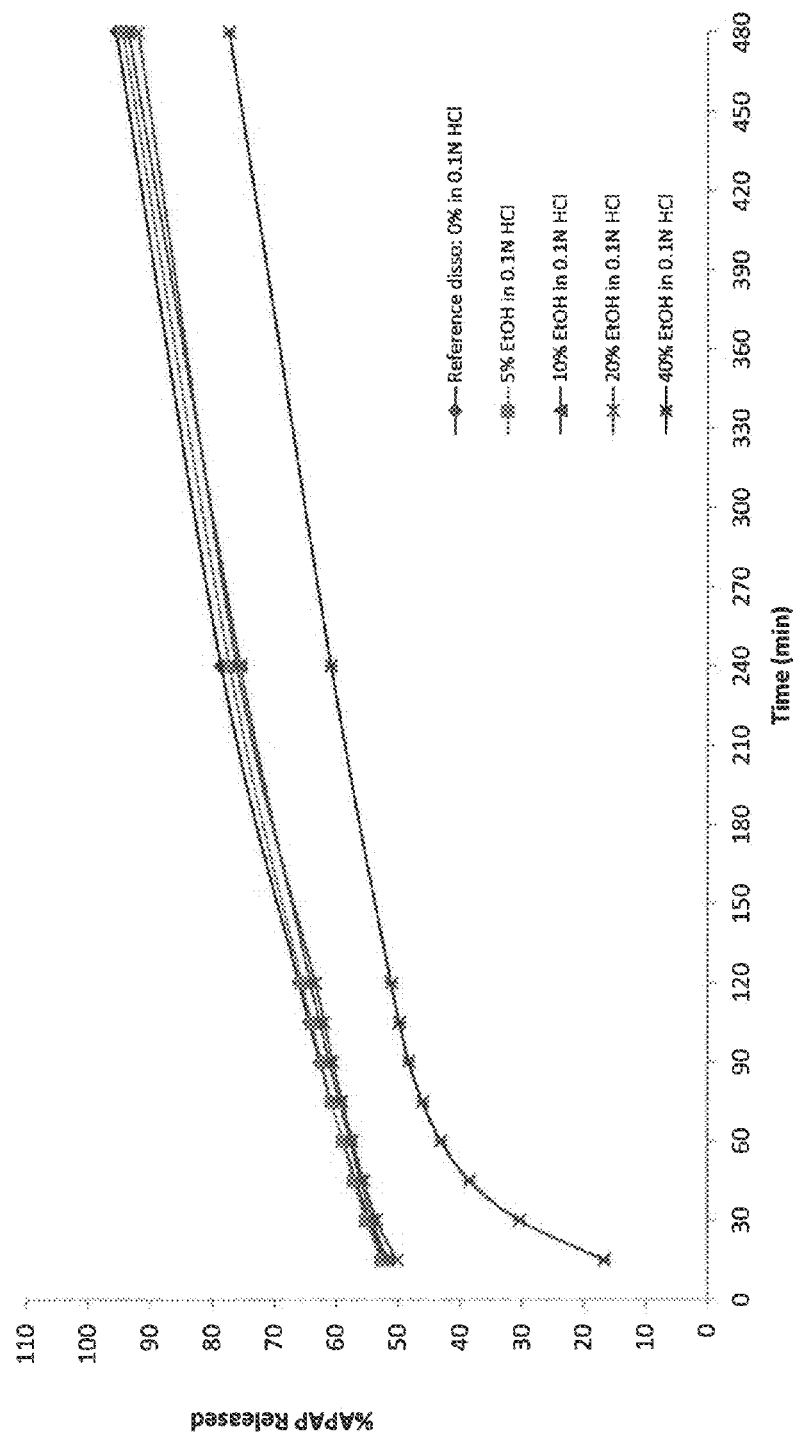


FIG. 60

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GASTRIC RETENTIVE EXTENDED RELEASE PHARMACEUTICAL COMPOSITIONS

RELATED CASES

This application claims priority to U.S. Provisional Application No. 61/487,047 filed on May 17, 2011, U.S. Provisional Application No. 61/537,533 filed on Sep. 21, 2011, and U.S. Provisional Application No. 61/606,896 filed on Mar. 5, 2012, which are incorporated herein by reference in their entirety to the full extent permitted by law.

FIELD OF THE INVENTION

The present disclosure relates to gastric retentive extended release pharmaceutical compositions comprising an opioid and an additional active pharmaceutical ingredient wherein the compositions may be administered under fed or fasted conditions.

BACKGROUND OF THE INVENTION

Oral drug administration remains the route of choice for the majority of clinical applications. Extended release (ER) dosage forms that are administered once or twice daily offer advantages over their immediate release (IR) counterparts because they reduce the magnitude of peaks and troughs of drug plasma concentration, provide longer dosing intervals, sustained analgesic effect, and increased patient compliance. For certain types of patients, such as those suffering from pain, these ER products can allow the patient to sleep through the night without having to wake up during the night to take the next dose. Thus, ER dosage forms can significantly increase the quality of life for such patients. Both IR and ER products for pain are widely available on the market. There are, however, no opioid/acetaminophen combination ER products available on the market.

Gastroretentive (GR) dosage formulations have demonstrated successful delivery of drugs for extended durations of action. One way to improve drug absorption is to hold a drug delivery system above the preferred absorption site or window (proximal small intestine), and maintain the drug release at an appropriate rate. For example, one strategy is to retain the formulation in the stomach (gastroretention). Over the last few decades, several gastroretentive drug delivery approaches have been designed and developed, including: high density (sinking) systems, which are retained in the bottom of the stomach, low density systems that float in gastric fluid due to buoyancy, mucoadhesive systems that release drugs following bio-adhesion to the gastric mucosa, superporous hydrogel systems, magnetic systems, and extendible or swellable systems that expand in the presence of water (gastric fluid) and fail to pass through the pyloric sphincter of stomach.

Parameters controlling the gastric retention of oral dosage forms include: density, size and shape of the dosage form, food intake and its nature (particularly fat content), total caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity, disease states of the individual (e.g., diabetes), and administration of drugs with impact on gastrointestinal transit time, for example, drugs acting as anticholinergic agents (e.g., atropine, propantheline), opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide, cisapride).

Food intake (i.e., viscosity of food, food volume, caloric value, and frequency of feeding) may have a profound effect

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on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the GRT of the dosage form and, thus, absorption increases because the drug stays at the preferred absorption site for a longer period of time. Indeed, GR formulations of the prior art should be administered with food in order to achieve the desired bioavailability.

There is a need, therefore, for extended release GR compositions comprising an opioid and a second active agent, wherein the release of the opioid is optimized to take advantage of the gastrointestinal effects of the opioid. The bioavailability of such composition is independent of food intake, thereby increasing the flexibility and ease of the administration of the composition.

SUMMARY OF THE INVENTION

Among the various aspects of the present disclosure is an extended release pharmaceutical composition comprising at least one extended release portion comprising an opioid, an additional active pharmaceutical ingredient, or a combination thereof, and at least one extended release component. At least one extended release portion comprises from about 60% to about 80% of the total amount of the opioid in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the opioid. Moreover, when the composition is orally administered to a subject, the opioid or the additional active pharmaceutical ingredient produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

A further aspect of the disclosure encompasses an extended release pharmaceutical composition comprising (a) at least one immediate release portion comprising an opioid, an additional active pharmaceutical ingredient, or a combination thereof, and (b) at least one extended release portion comprising an extended release component and an opioid, an additional active pharmaceutical ingredient, or a combination thereof. At least one immediate release portion comprises from about 20% to about 40% of the total amount of the opioid in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the opioid. Additionally, when the composition is orally administered to a subject, the opioid or the additional active pharmaceutical ingredient in the composition produce a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

Still another aspect of the disclosure provides a method for administering a gastric retentive pharmaceutical composition comprising an opioid to a subject in need thereof. The method comprises orally administering an effective amount of the gastric retentive composition to the subject, the subject being in a fasted state, wherein the opioid in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

Yet another aspect of the disclosure encompasses a method for treating pain in a subject in need thereof. The method comprises orally administering an effective amount of a gastric retentive pharmaceutical composition comprising an opioid to the subject in a fasted state, wherein the opioid in the composition produces a plasma profile characterized by at

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least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

Another aspect of the present disclosure is an extended release pharmaceutical composition comprising at least one extended release portion comprising oxycodone, acetaminophen, or a combination thereof, and at least one extended release component. At least one extended release portion comprises from about 60% to about 80% of the total amount of the oxycodone in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the oxycodone. Moreover, when the composition is orally administered to a subject, the oxycodone or the acetaminophen produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

A further aspect of the disclosure encompasses an extended release pharmaceutical composition comprising (a) at least one immediate release portion comprising oxycodone, acetaminophen, or a combination thereof, and (b) at least one extended release portion comprising an extended release component and oxycodone, acetaminophen, or a combination thereof. At least one immediate release portion comprises from about 20% to about 40% of the total amount of the oxycodone in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the oxycodone. Additionally, when the composition is orally administered to a subject, the oxycodone or the acetaminophen in the composition produce a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

Still another aspect of the disclosure provides a method for administering a gastric retentive pharmaceutical composition comprising oxycodone to a subject in need thereof. The method comprises orally administering an effective amount of the gastric retentive composition to the subject, the subject being in a fasted state, wherein the oxycodone in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

Yet another aspect of the disclosure encompasses a method for treating pain in a subject in need thereof. The method comprises orally administering an effective amount of a gastric retentive pharmaceutical composition comprising oxycodone to the subject in a fasted state, wherein the oxycodone in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

Other features and aspects of the disclosure are described in detail below.

REFERENCE TO COLOR FIGURES

This application file contains at least one drawing executed in color. Copies of this patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 presents the in vitro release profile of oxycodone from oxycodone-acetaminophen bilayer tablets comprising

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either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35% (w/w) POLYOX® 1105, 45% (w/w) POLYOX® 1105, or 45% (w/w) POLYOX® N60K, as indicated.

FIG. 2 shows the in vitro release profile of acetaminophen from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35% (w/w) POLYOX® 1105, 45% (w/w) POLYOX® 1105, or 45% (w/w) POLYOX® N60K, as indicated.

FIG. 3 presents the in vitro release profile of oxycodone from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

FIG. 4 presents the in vitro release profile of acetaminophen from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

FIG. 5 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval.

FIG. 6 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 7 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 8 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 9 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

FIG. 10 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treat-

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ment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

FIG. 11 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

FIG. 12 shows the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

FIG. 13 presents the mean plasma concentrations of oxycodone versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 14 shows the mean plasma concentrations of oxycodone versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 15 presents the mean plasma concentrations of acetaminophen versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 16 shows mean plasma concentrations of acetaminophen versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 17 illustrates the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 2 hours.

FIG. 18 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 2 hour period.

FIG. 19 shows the mean plasma concentrations of oxycodone as a function of time by treatment following oral administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 20 presents the mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 21 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet

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of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 22 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 23 shows a deconvolution plot of the biphasic absorption of oxycodone from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of oxycodone is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; squares represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and the immediate release 7.5 oxycodone/325 acetaminophen tablet is shown in a solid line with no symbols.

FIG. 24 presents a deconvolution plot of the biphasic absorption of acetaminophen from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of acetaminophen is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; triangles represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and squares represent the immediate release 7.5 oxycodone/325 acetaminophen product.

FIG. 25 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

FIG. 26 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

FIG. 27A is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation. FIG. 27B is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been

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doubled. FIG. 27C is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

FIG. 28A is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation. FIG. 28B is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled. FIG. 28C is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

FIG. 29A presents the mean plasma concentrations and Partial AUCs of acetaminophen (e.g., $AUC_{0-1.7h}$ and $AUC_{1.7-48h}$) versus time by the following treatments: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

FIG. 29B presents the mean plasma concentrations and Partial AUCs of oxycodone (e.g., AUC_{0-8h} and $AUC_{2.8-48h}$) versus time by the following treatments: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

FIG. 30A presents the mean plasma concentrations and Partial AUCs of oxycodone versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

FIG. 30B presents the mean plasma concentrations and Partial AUCs of acetaminophen versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

FIG. 31 presents the mean plasma concentrations of hydrocodone versus time by treatment for 0 to 36 hours. Treatment A (formulation A) was a single, two-tablet dose containing a total of 15 mg hydrocodone and 650 mg acetaminophen having slow release properties as compared to formulation B, administered orally under fasted conditions. Treatment B (formulation B) was a single, two-tablet dose containing a total of 15 mg hydrocodone and 650 mg acetaminophen having faster release properties as compared to formulation A, administered orally under fasted conditions. Treatment C (formulation B) was a single, two-tablet dose containing a total of 15 mg hydrocodone and 650 mg acetaminophen administered orally under fed conditions. Treatment D was one tablet of an immediate release 7.5 hydrocodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 32 presents the mean plasma concentrations of acetaminophen versus time by treatment for 0 to 36 hours. Treatment A (formulation A) was a single, two-tablet dose containing a total of 15 mg hydrocodone and 650 mg acetaminophen having slow release properties as compared to formulation B, administered orally under fasted conditions. Treatment B (formulation B) was a single, two-tablet dose containing a total of 15 mg hydrocodone and 650 mg acetaminophen having faster release properties as compared to formulation A, administered orally under fasted conditions. Treatment C (formulation B) was a single, two-tablet dose containing a total of 15 mg hydrocodone and 650 mg acetaminophen administered orally under fed conditions. Treatment

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D was one tablet of an immediate release 7.5 hydrocodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 33 presents the mean plasma concentrations of hydrocodone versus time by treatment as indicated in FIG. 31, but represented for 0 to 12 hours.

FIG. 34 presents the mean plasma concentrations of acetaminophen versus time by treatment as indicated in FIG. 32, but represented for 0 to 12 hours.

FIG. 35 presents simulated hydrocodone pharmacokinetic profiles at steady state versus time by treatment for 0 to 144 hours for Treatments A, B, C, and D of Example 16.

FIG. 36 presents simulated acetaminophen pharmacokinetic profiles at steady state versus time by treatment for 0 to 144 hours for Treatments A, B, C, and D of Example 16.

FIG. 37 presents mean plasma concentrations of hydrocodone as a function of time by treatment following oral administration of two tablets of 7.5 mg of hydrocodone and 325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 38 presents mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of two tablets of 7.5 mg of hydrocodone and 325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 39 presents mean plasma concentrations of hydrocodone as a function of time by treatment following oral administration of a single dose of Treatments A, B, and C of Example 18.

FIG. 40 presents mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of a single dose of Treatments A, B, and C of Example 18.

FIG. 41 presents mean plasma concentrations of hydrocodone as a function of time by treatment following oral administration of multiple doses of Treatments A, B, and C of Example 18.

FIG. 42 presents mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of multiple doses of Treatments A, B, and C of Example 18.

FIG. 43 presents dissolution data for the release of hydrocodone from fast-release, medium-release, and slow-release pharmaceutical compositions containing 7.5 mg hydrocodone and 325 acetaminophen.

FIG. 44 presents dissolution data for the release of acetaminophen from fast-release, medium-release, and slow-release pharmaceutical compositions containing 7.5 mg hydrocodone and 325 acetaminophen.

FIG. 45 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. Each formulation tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The ER portions of the three pharmaceutical formulations contained 25% by weight POLYOX® 205, 1105, and N-60K, respectively.

FIG. 46 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 45.

FIG. 47 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. Each formulation tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The ER portions of the three pharmaceutical formulations contained 45% by weight POLYOX® 205, 1105, and N-60K, respectively.

FIG. 48 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 47.

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FIG. 49 presents acetaminophen dissolution data for four pharmaceutical formulations described herein. Each formulation tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The ER portions of the four pharmaceutical compositions contained 25% by weight, 35% by weight, 45% by weight, and 55% by weight POLYOX® 1105, respectively.

FIG. 50 presents oxycodone HCl dissolution data for the four pharmaceutical formulations described in FIG. 49.

FIG. 51 presents acetaminophen dissolution data for five pharmaceutical formulations described herein. Each formulation tablet contained a total of 15 mg hydrocodone bitartrate HCl and a total of 500 mg acetaminophen. The ER portions of the five pharmaceutical formulations contained 25% by weight POLYOX® 205, 1105, N-12K, N-60K, and 301 respectively.

FIG. 52 presents hydrocodone bitartrate dissolution data for the five pharmaceutical formulations described in FIG. 51.

FIG. 53 presents acetaminophen dissolution data for five pharmaceutical formulations described herein. Each formulation tablet contained a total of 15 mg hydrocodone bitartrate and a total of 500 mg acetaminophen. The ER portions of the five pharmaceutical formulations contained 45% by weight POLYOX® 205, 1105, N-12K, N-60K, and 301 respectively.

FIG. 54 presents hydrocodone bitartrate dissolution data for the five pharmaceutical formulations described in FIG. 53.

FIG. 55 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. Each formulation tablet contained a total of 15 mg hydrocodone bitartrate and a total of 500 mg acetaminophen. The ER portions of the three pharmaceutical formulations contained 25% by weight, 35% by weight, and 45% by weight POLYOX® 1105, respectively.

FIG. 56 presents hydrocodone bitartrate dissolution data for the three pharmaceutical formulations described in FIG. 55.

FIG. 57 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. Each formulation tablet contained a total of 15 mg hydrocodone bitartrate and a total of 500 mg acetaminophen. The ER portions of the three pharmaceutical formulations contained 25% by weight, 35% by weight, and 45% by weight POLYOX® N-60K, respectively.

FIG. 58 presents hydrocodone bitartrate dissolution data for the three pharmaceutical formulations described in FIG. 57.

FIG. 59 presents the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 8 hours.

FIG. 60 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 8 hour period.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein is a gastric retentive extended release pharmaceutical composition comprising at least one opioid wherein gastric retention of the composition is achieved by a combination of a physical property of the composition and release of the opioid. In particular, the opioid is released at a rate that is sufficient to delay gastric emptying but insufficient

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to cause serious adverse gastrointestinal effects. Because gastric retention of the composition is aided by release of the opioid, oral administration of the composition is independent of food intake. That is, the composition may be administered to a subject in either a fed state or a fasted state. It was discovered that, upon oral administration to a subject, the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state. The food independence of this gastric retentive composition increases the convenience of administration of the composition in that it may be administered with or without food. Moreover, this property of the composition increases patient/subject compliance. The present disclosure also provides methods for administering the gastric retentive extended release composition disclosed herein, wherein the composition may be administered to a subject without regard to meals.

Headings included herein are simply for ease of reference, and are not intended to limit the disclosure in any way.

1. Definitions

Compounds useful in the compositions and methods include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, as well as racemic mixtures and pure isomers of the compounds described herein, where applicable.

When introducing elements of the various embodiment(s) of the present disclosure, the articles “a”, “an”, “the” and “said” are intended to mean that there are one or more of the elements. The terms “comprising”, “including” and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements.

The use of individual numerical values are stated as approximations as though the values were preceded by the word “about” or “approximately.” Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word “about” or “approximately.” In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms “about” and “approximately” when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words “about” or “approximately” will serve to broaden a particular numerical value or range. Thus, as a general matter, “about” or “approximately” broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term “about” or “approximately.” Consequently, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate

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value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

The term “abuse quotient” for a pharmaceutical composition as used herein is the numerical value obtained via dividing the C_{max} for a drug by the T_{max} for the same drug. Generally speaking, the abuse quotient provides a means for predicting the degree of addictiveness of a given pharmaceutical composition. Pharmaceutical compositions with lower abuse quotients typically are less addictive compared to pharmaceutical compositions with higher abuse quotients.

The term “active agent” or “drug” is used herein to refer to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor from eliciting a physiological response.

The term “bioequivalent,” as used herein, refers to two compositions, products or methods where the 90% Confidence Intervals (CI) for AUC, partial AUC and C_{max} are between 0.80 to 1.25.

The term “bulk density,” as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

The term “content uniformity,” as used herein refers to the testing of compressed tablets to provide an assessment of how uniformly the micronized or submicron active ingredient is dispersed in the powder mixture. Content uniformity is measured by use of USP Method (General Chapters, Uniformity of Dosage Forms), unless otherwise indicated. A plurality refers to five, ten or more tablet compositions.

The term “friability,” as used herein, refers to the ease with which a tablet will break or fracture. The test for friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of composition abraded or chipped is calculated.

The term “ER” as used herein refers to extended release. The phrases “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” are used interchangeably in this document. Further, as used herein the “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” can be either (i) a discrete part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

The term “IR” as used herein refers to immediate release. The phrases “immediate release layer,” “IR layer,” “IR portion” and “immediate release portion” are used interchangeably in this document. In addition, as used herein the “immediate release layer,” “IR layer,” “IR portion” and “immediate release portion” can be either (i) a discrete part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

The term “half life” as used herein refers to the time required for a drug’s blood or plasma concentration to decrease by one half. This decrease in drug concentration is a reflection of its excretion or elimination after absorption is complete and distribution has reached an equilibrium or quasi equilibrium state. The half life of a drug in the blood may be

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determined graphically off of a pharmacokinetic plot of a drug’s blood-concentration time plot, typically after intravenous administration to a sample population. The half life can also be determined using mathematical calculations that are well known in the art. Further, as used herein the term “half life” also includes the “apparent half-life” of a drug. The apparent half life may be a composite number that accounts for contributions from other processes besides elimination, such as absorption, reuptake, or enterohepatic recycling.

“Optional” or “optionally” means that the subsequently described element, component or circumstance may or may not occur, so that the description includes instances where the element, component, or circumstance occurs and instances where it does not.

“Partial AUC” means an area under the drug concentration-time curve (AUC) calculated using linear trapezoidal summation for a specified interval of time, for example, $AUC_{(0-1hr)}$, $AUC_{(0-2hr)}$, $AUC_{(0-4hr)}$, $AUC_{(0-6hr)}$, $AUC_{(0-8hr)}$, $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$, $AUC_{(0-(x)hr)}$, $AUC_{(x-yhr)}$, $AUC_{(T_{max}-t)}$, $AUC_{(0-(t)hr)}$, $AUC_{(T_{max} \text{ of IR product}+2SD)-t)}$, or $AUC_{(0-\infty)}$.

A drug “release rate,” as used herein, refers to the quantity of drug released from a dosage form or pharmaceutical composition per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically measured as an in vitro rate of dissolution, i.e., a quantity of drug released from the dosage form or pharmaceutical composition per unit time measured under appropriate conditions and in a suitable fluid. The specific results of dissolution tests claimed herein are performed on dosage forms or pharmaceutical compositions immersed in 900 mL of 0.1 N HCl using a USP Type II apparatus at a paddle speed of either about 100 rpm or about 150 rpm and a constant temperature of about 37° C. Suitable aliquots of the release rate solutions are tested to determine the amount of drug released from the dosage form or pharmaceutical composition. For example, the drug can be assayed or injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

The terms “subject” or “patient” are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, humans.

The term “tap density” or “tapped density,” as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

II. Gastric Retentive Extended Release Compositions

The present disclosure provides gastric retentive, extended release compositions comprising at least one opioid and at least one other active pharmaceutical ingredient (API) that is preferably absorbed in the upper gastrointestinal tract. In general, the gastric retentive, extended release composition comprises at least one extended release portion. The extended release portion(s) may comprise at least one opioid, at least one API, or combinations thereof. The gastric retentive, extended release composition disclosed herein may further comprise at least one immediate release portion. The immediate release portion(s) may comprise at least one opioid, at least one other API, or combinations thereof.

(a) Active Agents

The gastric retentive, extended release composition disclosed herein comprises at least one opioid and at least one additional API, each of which is discussed in more detail

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below. In one embodiment, the same opioid or combination of opioids is present in both the at least one immediate release portion and the at least one extended release portion of the composition; and the same API or combination of APIs is present in both the at least one immediate release portion and the at least one extended release portion of the composition.

(i) Opioids

The opioid(s) useful in the present invention include adullmine, alfentanil, allocryptopine, allylprodine, alphaprodine, anileridine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bezitramide, buprenorphine, bulbocaprone, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethyl methylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphine, papavereturn, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tapentadol, tilidine, tramadol, and pharmaceutical salts of any of the foregoing. In various embodiments, the extended release dosage form may comprise one, two, three, four, or more than four opioids. In another embodiment, the opioid is selected from the group consisting of oxycodone, hydrocodone, tramadol, codeine, and pharmaceutical salts of any of the foregoing. In yet another embodiment, opioid is selected from the group consisting of adullmine, alfentanil, allocryptopine, allylprodine, alphaprodine, anileridine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bezitramide, buprenorphine, bulbocaprone, butorphanol, clonitazene, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxymorphine, papavereturn, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tapentadol, tilidine, and pharmaceutical salts of any of the foregoing. In one embodiment, the extended release dosage form comprises one opioid.

In one embodiment, the composition may comprise from about 1.0 mg to about 500 mg of the opioid. In another embodiment, the composition may comprise from about 1.4 mg to about 400 mg of the opioid. In yet another embodiment, the amount of opioid in the composition may range from about 5 mg to about 300 mg. In still another embodiment, the amount of opioid in the composition may range from about 4 mg to about 30 mg. In another embodiment, the amount of opioid in the composition may range from about 30 mg to about 60 mg. In yet another embodiment, the amount of opioid in the composition may range from about 60 mg to about 120 mg.

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In an alternate embodiment, the amount of opioid in the composition may range from about 120 mg to about 300 mg. In various embodiments, the amount of opioid in the composition may be about 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg, 36 mg, 38 mg, 40 mg, 42 mg, 44 mg, 46 mg, 48 mg, 50 mg, 52 mg, 54 mg, 56 mg, 58 mg, 60 mg, 62 mg, 64 mg, 66 mg, 68 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 220 mg, 240 mg, 260 mg, 280 mg, 300 mg, 320 mg, 340 mg, 360 mg, 380 mg, or 400 mg. In one embodiment, the amount of opioid in the composition may range from about 7.5 mg to about 30 mg. In another embodiment, the amount of opioid in the composition may range from about 7.5 mg to about 15 mg. In still another embodiment, the amount of opioid in the composition may range from about 15 mg to about 30 mg.

(ii) Other Active Pharmaceutical Ingredient (API)

The gastric retentive, extended release composition disclosed herein may also comprise at least one other active pharmaceutical ingredient (API). In general, the other API is preferentially absorbed in the upper gastrointestinal tract (GIT). Accordingly, optimal absorption of the API may occur in the upper GIT (i.e., duodenum, jejunum, and ileum of the small intestine), with little or no absorption in the lower GIT (i.e., cecum and colon of the large intestine).

In some embodiments, the other API may be a non-opioid analgesic. Suitable non-opioid analgesics include acetaminophen (also known as paracetamol), acetylsalicylic acid, diclofenac, diflunisol, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, mefamanic acid, phenacetin, piroxicam, sulindac, and tolmetin. In other embodiments, the other API may be a steroidal anti-inflammatory agent such as celecoxib, deracoxib, ketoprofen, lumiracoxib, meloxicam, parecoxib, rofecoxib, or valdecoxib. In a further embodiment, the other API may be a steroidal anti-inflammatory agent such as alclometasone, dexamethasone, fluciclonide, hydrocortisone, methylprednisolone, prednisone, prednisolone, or triamcinolone. In further embodiments, the other API may be a norepinephrine transporter modulator such as tapentadol, a tricyclic antidepressant such as amitriptyline, an alpha-2 adrenergic agonist such as clonidine, a calcium channel blocker such as nimodipine, a GABA B agonist such as baclofen, a cannabinoid, a NMDA receptor antagonist, a CCK receptor antagonist, a beta blocker, or a serotonin receptor antagonist. Any of the aforementioned APIs may be in the form of a pharmaceutically acceptable salt. In various embodiments, the at least one extended release portion may comprise one, two, three, four, or more APIs. In one embodiment, one extended release portion may comprise one of the other APIs.

The amount of the other API in the gastric retentive, extended release composition can and will vary. In one embodiment, the composition may comprise from about 1.0 mg to about 1500 mg of the API. In another embodiment, the amount of API in the composition may range from about 100 mg to about 1000 mg. In another embodiment, the amount of API in the composition may range from about 50 mg to about 500 mg. In another embodiment, the amount of API in the composition may range from about 10 mg to about 100 mg. In yet another embodiment, the amount of API in the composition may range from about 1.0 mg to about 10 mg. In one embodiment, the amount of API in the composition may range from about 250 mg to about 1300 mg. In another embodiment, the amount of API in the composition may range from about 325 mg to about 650 mg. In still another

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embodiment, the amount of API in the composition may range from about 650 mg to about 1300 mg.

(b) Immediate Release Portion

The gastric retentive, extended release composition disclosed herein may comprise at least one immediate release portion. The at least one immediate release portion may comprise at least one opioid, at least one other API, or combinations thereof.

The at least one immediate release portion of the composition is designed to release more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion within about one hour. In one embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 45 minutes. In another embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 30 minutes. In a further embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 20 minutes. In yet another embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 15 minutes. In an alternate embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 10 minutes. In yet another embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 5 minutes.

In some embodiments, the immediate release portion may be part of or homogeneously mixed with the extended release portion.

(i) Opioid(s)

At least one immediate release portion of the gastric retentive, extended release composition may comprise at least one opioid. Suitable opioids are detailed above in section (II)(a) (i). In one embodiment, the opioid may be codeine or a salt thereof. In another embodiment, the opioid may be hydrocodone or a salt thereof. In yet another embodiment, the opioid may be hydromorphone or a salt thereof. In still another embodiment, the opioid may be morphine or a salt thereof. In a further embodiment, the opioid may be oxycodone or a salt thereof. In an alternate embodiment, the opioid may be tramadol or a salt thereof. In another embodiment, the opioid may be oxycodone or a salt thereof.

The amount of opioid present in the at least one immediate release portion of the composition can and will vary. In one embodiment, the amount of opioid in the at least one immediate release portion may range from about 0.4 mg to about 100 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.25 mg to about 75 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1 mg to about 20 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may range from about 0.5 mg to about 10 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 7.5 mg to about 15 mg. In yet another embodiment, the amount of opioid in the at least one immediate release portion may range from about 15 mg to about 30 mg. In an alternate embodiment, the amount of opioid in the at least one immediate release portion may range from about 30 mg to about 75 mg.

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In various embodiments, the amount of opioid in the at least one immediate release portion may be about 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 12.5 mg, 15 mg, 16 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 40 mg, 75 mg, or 100 mg. In one embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 2.0 mg, for example, about 1.875 mg. In yet another embodiment, the amount of opioid in the at least one immediate release portion may range from about 2.0 mg and about 3.0 mg, for example, about 2.25 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 3.0 mg and about 4.0 mg, for example, about 3.75 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may range from about 7.0 mg and about 8.0 mg, for example, about 7.5 mg.

The amount of opioid present in the at least one immediate release portion may be expressed as a percentage (w/w) of the total amount of opioid in the composition. At least one immediate release portion may comprise from about 20% to about 40% (w/w) of the total amount of opioid present in the composition. In certain embodiments, the percentage of opioid present in the at least one immediate release portion of the composition may be about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, or 40% (w/w) of the total amount of opioid present in the composition. In one embodiment, the percentage of opioid present in the at least one immediate release portion may range from about 20% to about 30% (w/w) of the total amount of opioid present in the composition. In another embodiment, the percentage of opioid present in the at least one immediate release portion may be about 25% (w/w) of the total amount of opioid present in the composition.

The amount of opioid in an immediate release portion also may be expressed as a percentage (w/w) of the total weight of such immediate release portion of the composition. In one embodiment, the amount of opioid in an immediate release portion may range from about 0.2% (w/w) to about 20% (w/w) of the total weight of such immediate release portion of the composition. In another embodiment, the amount of opioid in an immediate release portion may range from about 0.5% (w/w) to about 5% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion may comprise an amount of opioid that is approximately 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.25%, 7.5%, 7.75%, 8.0%, 8.25%, 8.5%, 8.75%, 9.0%, 9.25%, 9.5%, 9.75%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% (w/w) of the total weight of such immediate release portion of the composition. In one embodiment, the amount of opioid in an immediate release portion may be about 0.5% to about 1.0% (w/w) of the total weight of such immediate release portion of the composition.

In some embodiments, the opioid in the at least one immediate release portion of the dosage form may be in the form of

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particles comprising opioid and at least one excipient. The at least one immediate release portion, therefore, may comprise particles of opioid(s) that are admixed with other API(s) and optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety. The opioid particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Other API(s)

At least one immediate release portion of the composition may comprise at least one other API. Examples of suitable APIs that may be included in the at least one immediate release portion are presented above in section (II)(a)(ii). In one embodiment, the other API may be acetylsalicylic acid or a salt thereof. In another embodiment, the other API may be diclofenac or a salt thereof. In yet another embodiment, the other API may be ibuprofen or a salt thereof. In still another embodiment, the other API may be indomethacin or a salt thereof. In a further embodiment, the other API may be ketoprofen or a salt thereof. In an alternate embodiment, the other API may be naproxen or a salt thereof. In another embodiment, the other API may be piroxicam or a salt thereof. In still another embodiment, the other API may be prednisolone or a salt thereof. In one embodiment, the other API may be acetaminophen or salt thereof.

The amount of the other API in the at least one immediate release portion can and will vary. In one embodiment, the immediate release portion may comprise from about 0.5 mg to about 750 mg of the API. In another embodiment, the amount of API in the at least one immediate release portion may range from about 50 mg to about 500 mg. In another embodiment, the amount of API in the at least one immediate release portion may range from about 25 mg to about 250 mg. In another embodiment, the amount of API in the at least one immediate release portion may range from about 150 mg to about 500 mg. In yet another embodiment, the amount of API in the at least one immediate release portion may range from about 0.5 mg to about 5 mg. In one embodiment, the amount of API in the at least one immediate release portion may range from about 125 mg to about 650 mg. In another embodiment, the amount of API in the at least one immediate release portion may range from about 162.5 mg to about 325 mg. In still another embodiment, the amount of API in the at least one immediate release portion may range from about 325 mg to about 650 mg.

The amount of other API in the at least one immediate release portion of the gastric retentive, extended release composition can and will vary. In general, the amount of other API present in the at least one immediate release portion may range from about 30% to about 70% (w/w) of the total amount of other API in the composition. In one embodiment, the amount of other API present in the at least one immediate release portion ranges from about 40% to about 60% (w/w) of the total amount of API in the composition. In various embodiments, the at least one immediate release portion of the composition may comprise about 30%, 31%, 32%, 33%,

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34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70% (w/w) of the total amount of API in the composition.

The amount of other API in an immediate release portion of the composition may range from about 15% to about 95% (w/w) of the total weight of such immediate release portion of the composition. In various embodiments, the amount of other API(s) in an immediate release portion may be about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 82%, 84%, 86%, 88%, 90%, 92%, or 95% (w/w) of the total weight of such immediate release portion.

In embodiments in which the other API is acetaminophen, the amount of acetaminophen in the at least one immediate release portion may range from about 40 mg to about 800 mg. In another embodiment, the at least one immediate release portion of the composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one immediate release portion may comprise from about 150 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 320 mg, 325 mg, 330 mg, 335 mg, 340 mg, 345 mg, 350 mg, 355 mg, 360 mg, 365 mg, 370 mg, 375 mg, 380 mg, 385 mg, 390 mg, 395 mg, 400 mg, 500 mg, 520 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 780 mg. In one embodiment, the at least one immediate release portion may comprise about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 125 mg.

The at least one immediate release portion of the composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the gastric retentive composition. The amount of acetaminophen in the at least one immediate release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the composition. In one embodiment, the percentage of acetaminophen present in the at least one immediate release portion may be about 50% (w/w) of the total amount of acetaminophen present in the composition.

The amount of acetaminophen in an immediate release portion of the pharmaceutical composition may range from about 20% to about 95% (w/w) of the total weight of such immediate release portion of the composition. In various embodiments, an immediate release portion may comprise a dose of acetaminophen that is approximately about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%,

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93%, 94%, or 95% (w/w) of the total weight of such immediate release portion. In one embodiment, the amount of acetaminophen in an immediate release portion may range from about 70% to about 80% (w/w) of the total weight of such immediate release portion of the composition.

(iii) Excipients

The at least one immediate release portion of the gastric retentive, extended release composition may further comprise at least one excipient. Suitable excipients include binders, fillers, disintegrants, lubricants, antioxidants, chelating agents, and color agents.

In one embodiment, the at least one immediate release portion of the composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxycellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an immediate release portion of the composition may range from about 5% to about 10% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the composition may comprise at least one binder that is present in an amount that is about 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.2%, 8.4%, 8.6%, or 8.8% (w/w) of such immediate release portion of the composition.

In another embodiment, the at least one immediate release portion of the composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an immediate release portion may range from about 1.0% to about 10.0% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the composition may comprise at least one filler that is present in an amount that is about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.1%, 6.2%, 6.3%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, or 10.0%, (w/w) of such immediate release portion of the composition.

In still another embodiment, the at least one immediate release portion of the composition may further comprise at least one disintegrant. The disintegrant may be selected from the group consisting of croscarmellose sodium, crospovidone, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, low substituted hydroxypropylcellulose, microcrystalline cellulose, and sodium starch glycolate. In one embodiment, the amount of disintegrant in an immediate release portion may range from about 2.0% to about 15.0% (w/w) of the total weight of such immediate release portion. In some embodiments, the amount of disin-

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tegrant in an immediate release portion may be about 4.0%, 4.2%, 4.4%, 4.6%, 4.8%, 5.0%, 5.2%, 5.4%, 5.6%, 5.8%, 6.0%, 6.2%, 6.4%, 6.6%, 6.8%, or 7.0% (w/w) of such immediate release portion of the composition.

In a further embodiment, the at least one immediate release portion of the composition may further comprise at least one lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of an immediate release portion. In certain embodiments, the amount of lubricant in an immediate release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.55%, 1.6%, 1.65%, 1.7%, 1.75%, 1.80%, 1.85%, 1.90%, 1.95%, or 2.0% (w/w) of the total weight of such immediate release portion.

In yet another embodiment, the at least one immediate release portion of the composition may comprise at least one antioxidant. Suitable antioxidants include, without limitation, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, and propylgallate. The amount of antioxidant present in an immediate release portion of the composition may range from about 0.01% to about 4.0% (w/w), or from about 0.02% to about 0.10% (w/w) of the total weight of such immediate release portion. In various embodiments, the amount of antioxidant present in an immediate release portion of the composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such immediate release portion.

In still another embodiment, the at least one immediate release portion of the composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxyethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetracetic acid, 1,4,7,1-tetraazacyclodecane-N,N',N'',N'''-tetracetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N''-tri-acetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,1-tetraazacyclodecane, 1,4,7-triazacyclonane-N,N',N''-tri-acetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N',N'-tetraacetic acid. In one embodiment, the chelating agent may be the sodium salt of EDTA. The amount of chelating agent present in an immediate release portion of the composition may range from about 0.001% to about 0.20% (w/w) of such immediate release portion. In some embodiments, the amount of chelating agent present in an immediate release portion of the composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such immediate release portion.

In an alternate embodiment, the at least one immediate release portion of the composition may comprise at least one color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic col-

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ors (Ext. D&C). In various embodiments, the amount of color agent present in an immediate release portion may range from about 2.0% to about 5.0% (w/w) of the total weight of such immediate release portion of the composition. In other embodiments, the amount of color agent present in an immediate release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of the total weight of such immediate release portion.

(c) Extended Release Portion

The gastric retentive, extended release composition disclosed herein comprises at least one extended release portion. The at least one extended release portion may comprise at least one opioid, at least one other API, or combinations thereof. The at least one extended release portion further comprises at least one extended release component. The extended release component may comprise at least one extended release polymer.

The at least one extended release portion of the composition is designed to release the opioid(s) and the other API(s) over an extended period of time. In general, the at least one extended release portion provides release of the opioid(s) and/or the API(s) for a period of time ranging from at least about 4 hours (hrs) to at least about 12 hrs. In one embodiment, the opioid(s) and/or the other API(s) may be released from the at least one extended release portion composition over a period of time of at least about 5 hours, or over a period of at least about 6 hours. In another embodiment, the at least one extended release portion may release the opioid(s) and/or the other API(s) over a period of at least about 7 hours, or a period of at least about 8 hours. In still another embodiment, the opioid(s) and/or the other API(s) may be released from the at least one extended release portion over a period of at least about 9 hours, or over a period of at least about 10 hours. In a further embodiment, the at least one extended release portion may release the opioid(s) and/or the other API(s) over a period of at least about 11 hours, or over a period of at least about 12 hours.

(i) Opioids

At least one extended release portion of the gastric retentive, extended release composition comprises at least one opioid. Suitable opioids are detailed above in section (II)(a) (i). In one embodiment, the opioid may be codeine or a salt thereof. In another embodiment, the opioid may be hydrocodone or a salt thereof. In yet another embodiment, the opioid may be hydromorphone or a salt thereof. In still another embodiment, the opioid may be morphine or a salt thereof. In a further embodiment, the opioid may be oxycodone or a salt thereof. In an alternate embodiment, the opioid may be tramadol or a salt thereof. In another embodiment, the opioid may be oxycodone or a salt thereof.

The amount of opioid present in the at least one extended release portion of the gastric retentive, extended release composition can and will vary. In one embodiment, the amount of opioid in the at least one extended release portion may range from about 1 mg to about 300 mg. In another embodiment, the amount of opioid in the at least one extended release portion may range from about 3.75 mg to about 225 mg. In a further embodiment, the at least one extended release portion of the composition may comprise from about 1 mg to about 22.5 mg of opioid. In another embodiment, the amount of opioid in the at least one extended release portion may be from about 22.5 mg to about 45 mg. In yet another embodiment, the amount of opioid in the at least one extended release portion may be from about 45 mg to about 90 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may be from about 90 mg to about 225 mg. In yet another embodiment, the amount of opioid in the at least one

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extended release portion may be about 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 5.625 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10.0 mg, 10.5 mg, 11.0 mg, 11.25 mg, 11.5 mg, 12.0 mg, 12.5 mg, 13.0 mg, 13.5 mg, 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 35 mg, 40 mg, 45 mg, or 50 mg. In one embodiment, the amount of opioid in the at least one extended release portion may be from about 5 mg to about 6 mg, for example, about 5.625 mg. In another embodiment, the amount of opioid in the at least one extended release portion may be from about 10 mg to about 12 mg, for example, about 11.25 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may be from about 22 mg to about 23 mg, for example, about 22.5 mg.

The amount of opioid present in the at least one extended release portion may be expressed as a percentage of the total amount of opioid in the gastric retentive, extended release composition. In one embodiment, the at least one extended release portion of the composition comprises from about 60% to about 80% (w/w) of the total amount of opioid present in the gastric retentive, extended release composition. In certain embodiments, the percentage of opioid present in the at least one extended release portion of the composition may be about 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% (w/w) of the total amount of opioid present in the composition. In one embodiment, the percentage of opioid present in the at least one extended release portion of the pharmaceutical composition may be about 75% of the total amount of opioid present in the composition.

The amount of opioid in an extended release portion also may be expressed as a percentage of the total weight of such extended release portion of the composition. In one embodiment, the amount of opioid in an extended release portion may range from about 0.3% to about 8.0% (w/w) of the total weight of such extended release portion of the composition. In various embodiments, an extended release portion may comprise an amount of opioid that is approximately 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, or 8% (w/w) of the total weight of such extended release portion of the composition. In one embodiment, the amount of opioid in an extended release portion may comprise about 0.5% to about 2% (w/w) of the total weight of such extended release portion of the composition.

In some embodiments, the opioid of the at least one extended release portion of the composition may be in the form of particles comprising the opioid and at least one excipient. Thus, the at least one extended release portion may comprise particles of opioid(s) which are admixed with the additional API(s) and the extended release component, both of which are detailed below, as well as optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety. The opioid particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the d₉₀ of the particles may be about 40 microns, 50 microns, 100 microns, 150

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microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the d90 of the particles may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Other API(s)

The at least one extended release portion of the gastric retentive, extended release composition may comprise at least one other API. Examples of suitable APIs that may be included in the at least one extended release portion are presented above in section (I)(a)(ii). In one embodiment, the other API may be acetylsalicylic acid or a salt thereof. In another embodiment, the API may be diclofenac or a salt thereof. In yet another embodiment, the API may be ibuprofen or a salt thereof. In still another embodiment, the API may be indomethacin or a salt thereof. In a further embodiment, the API may be ketoprofen or a salt thereof. In an alternate embodiment, the API may be naproxen or a salt thereof. In another embodiment, the API may be piroxicam or a salt thereof. In still another embodiment, the API may be prednisolone or a salt thereof. In one embodiment, the API may be acetaminophen or salt thereof.

The amount of the other API in the at least one extended release portion can and will vary. In one embodiment, the at least one extended release portion may comprise from about 0.5 mg to about 750 mg of the API. In another embodiment, the amount of API in the at least one extended release portion may range from about 50 mg to about 500 mg. In another embodiment, the amount of API in the at least one extended release portion may range from about 25 mg to about 250 mg. In another embodiment, the amount of API in the at least one extended release portion may range from about 150 mg to about 500 mg. In yet another embodiment, the amount of API in the at least one extended release portion may range from about 0.5 mg to about 5 mg. In one embodiment, the amount of API in the at least one extended release portion may range from about 125 mg to about 650 mg. In another embodiment, the amount of API in the at least one extended release portion may range from about 162.5 mg to about 325 mg. In still another embodiment, the amount of API in the at least one extended release portion may range from about 325 mg to about 650 mg.

The amount of other API(s) in the at least one extended release portion of the gastric retentive, extended release composition can and will vary, depending upon the identity of the API(s). In general, the amount of other API present in the at least one extended release portion may range from about 30% to about 70% (w/w) of the total amount of other API in the composition. In one embodiment, the amount of other API present in the at least one extended release portion may range from about 40% to about 60% (w/w) of the total amount of other API in the composition. In various embodiments, the at least one extended release portion of the retentive, extended release composition may comprise about 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70% (w/w) of the total amount of other API in the composition.

The amount of other API in an extended release portion also may be expressed as a percentage of the total weight of such extended release portion of the retentive, extended release composition. In various embodiments, the amount of other API in an extended release portion may range from about 10% to about 70% (w/w) of the total weight of such extended release portion of the composition. In various embodiments, the amount of other API in an extended release

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portion may be about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 32%, 34%, 36%, 38%, 40%, 42%, 44%, 46%, 48%, 50%, 52%, 54%, 56%, 58%, 60%, 62%, 64%, 66%, 68%, or 70% (w/w) of the total weight of such extended release portion of the composition.

In embodiments in which the other API is acetaminophen, the amount of acetaminophen in the at least one extended release portion may range from about 40 mg to about 800 mg. In one embodiment, the at least one extended release portion of the composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one extended release portion may comprise from about 150 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one extended release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 800 mg.

In one embodiment, the at least one extended release portion may comprise about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 125 mg.

The amount of acetaminophen in the at least one extended release portion may range from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the composition. In various embodiments, the amount of acetaminophen in the at least one extended release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the gastric retentive, extended release composition. In one embodiment, the percentage of acetaminophen present in the at least one extended release portion of the composition may be about 50% (w/w) of the total amount of acetaminophen present in the composition.

The amount of acetaminophen in an extended release portion of the composition may range from about 15% to about 60% (w/w) of the total weight of such extended release portion of the composition. In various embodiments, the amount of acetaminophen in an extended release portion may be about 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 32%, 35%, 37%, 40%, 42%, 45%, 47%, 50%, 52%, 55%, 57%, or 60% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of acetaminophen in an extended release portion may range from about 20% to about 40% (w/w) of the total weight of such extended release portion of the composition.

(iii) Extended Release Component

The at least one extended release portion of the gastric retentive, extended release composition also comprises at least one extended release component. Suitable extended release components include polymers, resins, hydrocolloids, hydrogels, and the like.

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In one embodiment, the at least one extended release component comprises at least one extended release polymer. Suitable polymers for inclusion in the at least one extended release portion of the gastric retentive, extended release composition may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, such as random copolymers, block copolymers, and graft copolymers. Suitable hydrophilic polymers include, but are not limited to: polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers; cellulosic polymers, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, microcrystalline cellulose, and polysaccharides and their derivatives; acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate; maleic anhydride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropylacrylamide); polyalkylene oxides; poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; xanthan gum; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate. The polymers may be used individually or in combination. Certain combinations may provide a more controlled release of opioid(s) and API(s) than their components when used individually. Suitable combinations include cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum, and poly(ethylene oxide) combined with xanthan gum.

In one embodiment, the at least one extended release polymer may be a cellulosic polymer, such as an alkyl substituted cellulose derivative as detailed above. In terms of their viscosities, one class of preferred alkyl substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C.

In one embodiment, the at least one extended release polymer may be a polyalkylene oxide. In another aspect, the polyalkylene oxide may be poly(ethylene oxide). In a further embodiment, the poly(ethylene oxide) may have an approximate molecular weight between 500,000 Daltons (Da) to about 10,000,000 Da or about 900,000 Da to about 7,000,000 Da. In yet a further embodiment, the poly(ethylene oxide) may have a molecular weight of approximately about 600,

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000 Da, about 700,000 Da, about 800,000 Da, about 900,000 Da, about 1,000,000 Da, about 2,000,000 Da, about 3,000,000 Da, about 4,000,000 Da, about 5,000,000 Da, about 6,000,000 Da, about 7,000,000 Da, about 8,000,000 Da, 9,000,000 Da, or 10,000,000 Da.

In another embodiment, the polyethylene oxide may be any desirable grade of POLYOX™ or any combination thereof. By way of example and without limitation, the POLYOX™ grade may be WSR N-10, WSR N-80, WSR N-750, WSR 205, WSR 1105, WSR N-12K, WSR N-60K, WSR-301, WSR Coagulant, WSR-303, WSR-308, WSR N-3000, UCARFLOC Polymer 300, UCARFLOC Polymer 302, UCARFLOC Polymer 304, and UCARFLOC Polymer 309. In one embodiment, the polyethylene oxide may have an average molecular weight of from about 100,000 Da to about 8,000,000 Da. In another embodiment, the polyethylene oxide may have an average molecular weight of about 100,000 Da, about 200,000 Da, about 300,000 Da, about 400,000 Da, about 500,000 Da, about 600,000 Da, about 700,000 Da, about 800,000 Da, about 900,000 Da, about 1,000,000 Da, about 2,000,000 Da, about 3,000,000 Da, about 4,000,000 Da, about 5,000,000 Da, about 6,000,000 Da, about 7,000,000 Da, or about 8,000,000 Da. In still another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units ($-\text{CH}_2\text{CH}_2\text{O}-$) of about 2,000 to about 160,000. In yet another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units of about 2,275, about 4,500, about 6,800, about 9,100, about 14,000, about 20,000, about 23,000, about 45,000, about 90,000, about 114,000, or about 159,000.

The release profile of the extended release compositions disclosed herein will depend partially upon the molecular weight of the polymer. The polymers are preferably of a moderate to high molecular weight (900,000 Da to 4,000,000 Da) to provide control release of the opioid(s) and/or the API(s) from the composition via diffusion of the opioid(s) and/or other API(s) out of the polymer and/or erosion of the polymer. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of about 900,000 Da to about 2,000,000 Da. Using a lower molecular weight ("MW") polyethylene oxide, such as POLYOX® 1105 (900,000 MW), the release rates for all active agents generally will be higher. Using a higher molecular weight polyethylene oxide (such as POLYOX® N-60K (2,000,000 MW) or POLYOX® WSR-301 (4,000,000 MW) generally reduces the rate of release for all active agents. In another embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight may be utilized such that the viscosity of a 2% aqueous solution may be about 4000 cps to greater than about 100,000 cps.

The release profile of the extended release pharmaceutical composition disclosed herein may also depend upon the amount of the extended release polymer(s) in the pharmaceutical composition. In general, the release rates for all active agents may be decreased by increasing the amount of the extended release polymer(s) in the pharmaceutical composition. By way of example and without limitation, the release profile of all active agents may be decreased by increasing the amount of POLYOX® 1105 from about 25% by weight of the ER portion to about 35% by weight of the ER portion.

The amount of polymer or polymers present in the at least one extended release portion of the composition can and will vary. In one embodiment, the polymer present in an extended release portion of the gastric retentive, extended release composition may range from about 15% to about 70% (w/w), or about 20% to about 60% (w/w), or about 25% to about 55%

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(w/w) of the total weight of such extended release portion of the composition. In another embodiment, the amount of polymer present in an extended release portion of the composition may range from about 30% to about 50% (w/w) of the total weight of such extended release portion. In still another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 35% to about 45% (w/w) of the total weight of such extended release portion. In yet another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 30%, 35%, 40%, 45%, 50%, 55%, or 60% (w/w) of the total weight of such extended release portion. In still another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 35% (w/w) of the total weight of such extended release portion. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 45% (w/w) of the total weight of such extended release portion.

(iv) Excipients

The at least one extended release portion of the gastric retentive, extended release composition may further comprise at least one excipient. Suitable excipients include binders, fillers, lubricants, antioxidants, chelating agents, and color agents.

In one embodiment, the at least one extended release portion of the composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxycellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an extended release portion of the composition may range from about 0.5% to about 8.0% (w/w) of such extended release portion. In various embodiments, an extended release portion of the composition may comprise at least one binder that is present in an amount that is about 0.5%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, or 6.0% (w/w) of such extended release portion of the composition.

In another embodiment, the at least one extended release portion of the composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate; carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an extended release portion may range from about 2% to about 50% (w/w) of the total weight of such extended release portion. In various embodiments, an extended release portion of the dosage form may comprise at least one filler that is present in an amount that is about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%,

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35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, or 50% (w/w) of such extended release portion of the composition.

In a further embodiment, the at least one extended release portion of the composition may further comprise at least one lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of an extended release portion. In certain embodiments, the amount of lubricant in an extended release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.75%, 1.80%, 1.85%, 1.90%, or 2.0% (w/w) of the total weight of such extended release portion of the composition.

In yet another embodiment, the at least one extended release portion of the composition may comprise at least one antioxidant. Suitable antioxidants include, without limit, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, and propylgallate. The amount of antioxidant present in an extended release portion of the composition may range from about 0.01% to about 4.0% (w/w), or from about 0.02% to about 0.10% (w/w). In various embodiments, the amount of antioxidant present in an extended release portion of the composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such extended release portion.

In still another embodiment, the at least one extended release portion of the composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxyethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetraacetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N'',N'''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicycysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N'',N'''-tetraacetic acid. In one embodiment, the chelating agent may be the sodium salt of EDTA. The amount of chelating agent present in an extended release portion of the composition may range from about 0.001% to about 0.20% (w/w) of such extended release portion. In some embodiments, the amount of chelating agent present in an extended release portion may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% of the total weight of such extended release portion.

In an alternate embodiment, the at least one extended release portion of the composition may comprise at least one color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an extended release portion may range from

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about 2.0% to about 5.0% (w/w) of such extended release portion of the composition. In other embodiments, the amount of color agent present in an extended release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of such extended release portion.

(d) Gastric Retention

The opioid containing extended release composition disclosed herein has gastric retentive properties. In general, the gastric retentive properties of the composition are due to a combination of a physical property of the composition and release of the opioid.

(i) Physical Properties

A. Size of the Composition

The physical property of the composition that leads to gastric retention can and will vary. In one embodiment, the physical property of the composition that results in gastric retention may be the physical size of the composition. That is, the composition may have a size that is small enough to be orally ingested and enter the stomach, but large enough to prevent passage through the pyloric sphincter into the small intestine. In some embodiments in which the composition is designed for humans, the composition may have a length (or diameter) of more than about 7 mm, 8 mm, 9 mm, or 10 mm. In other embodiments in which the composition is designed for humans, the composition may have a length (or diameter) of more than about 11 mm, 12 mm, or 13 mm, 14 mm, 15 mm, 16 mm, 17 mm, 18 mm, 19 mm, 20 mm or longer. In still other embodiments, the composition may have (i) a length of approximately 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, or 20 mm as measured on the major axis, (ii) a width of approximately 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, or 13 mm as measured on the minor axis, and (iii) a height or thickness of approximately 5 mm, 5.1 mm, 5.2 mm, 5.3 mm, 5.4 mm, 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, or 6 mm. In yet another embodiment, the composition may have (i) a length of approximately 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, or 19.3 mm as measured on the major axis, (ii) a width of approximately 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, or 12.5 mm as measured on the minor axis, and (iii) a height or thickness of approximately 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, or 5.8 mm. In general, such compositions are designed to degrade, disintegrate, decrease in size, or collapse in a specified time interval (e.g., dosing interval) such that they may pass through the pyloric valve or be evacuated from the stomach by a housekeeper wave of gastric contractions.

In still other embodiments, prior to administration to a patient or immersion in fluid, the pharmaceutical composition may have (i) a length of approximately 18 mm, 18.01 mm, 18.02 mm, 18.03 mm, 18.04 mm, 18.05 mm, 18.06 mm, 18.07 mm, 18.08 mm, 18.09 mm, 18.1 mm, 18.11 mm, 18.12 mm, 18.13 mm, 18.14 mm, 18.15 mm, 18.16 mm, 18.17 mm, 18.18 mm, 18.19 mm, 18.2 mm, 18.21 mm, 18.22 mm, 18.23 mm, 18.24 mm, 18.25 mm, 18.26 mm, 18.27 mm, 18.28 mm, 18.29 mm, 18.3 mm, 18.31 mm, 18.32 mm, 18.33 mm, 18.34 mm, 18.35 mm, 18.36 mm, 18.37 mm, 18.38 mm, 18.39 mm, 18.4 mm, 18.41 mm, 18.42 mm, 18.43 mm, 18.44 mm, 18.45 mm, 18.46 mm, 18.47 mm, 18.48 mm, 18.49 mm, 18.5 mm, 18.51 mm, 18.52 mm, 18.53 mm, 18.54 mm, 18.55 mm,

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18.56 mm, 18.57 mm, 18.58 mm, 18.59 mm, 18.6 mm, 18.61 mm, 18.62 mm, 18.63 mm, 18.64 mm, 18.65 mm, 18.66 mm, 18.67 mm, 18.68 mm, 18.69 mm, 18.7 mm, 18.71 mm, 18.72 mm, 18.73 mm, 18.74 mm, 18.75 mm, 18.76 mm, 18.77 mm, 18.78 mm, 18.79 mm, 18.8 mm, 18.81 mm, 18.82 mm, 18.83 mm, 18.84 mm, 18.85 mm, 18.86 mm, 18.87 mm, 18.88 mm, 18.89 mm, 18.9 mm, 18.91 mm, 18.92 mm, 18.93 mm, 18.94 mm, 18.95 mm, 18.96 mm, 18.97 mm, 18.98 mm, 18.99 mm, 19 mm, 19.01 mm, 19.02 mm, 19.03 mm, 19.04 mm, 19.05 mm, 19.06 mm, 19.07 mm, 19.08 mm, 19.09 mm, 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, 19.3 mm, 19.31 mm, 19.32 mm, 19.33 mm, 19.34 mm, 19.35 mm, 19.36 mm, 19.37 mm, 19.38 mm, 19.39 mm, 19.4 mm, 19.41 mm, 19.42 mm, 19.43 mm, 19.44 mm, 19.45 mm, 19.46 mm, 19.47 mm, 19.48 mm, 19.49 mm, 19.5 mm, 19.51 mm, 19.52 mm, 19.53 mm, 19.54 mm, 19.55 mm, 19.56 mm, 19.57 mm, 19.58 mm, 19.59 mm, 19.6 mm, 19.61 mm, 19.62 mm, 19.63 mm, 19.64 mm, 19.65 mm, 19.66 mm, 19.67 mm, 19.68 mm, 19.69 mm, 19.7 mm, 19.71 mm, 19.72 mm, 19.73 mm, 19.74 mm, 19.75 mm, 19.76 mm, 19.77 mm, 19.78 mm, 19.79 mm, 19.8 mm, 19.81 mm, 19.82 mm, 19.83 mm, 19.84 mm, 19.85 mm, 19.86 mm, 19.87 mm, 19.88 mm, 19.89 mm, 19.9 mm, 19.91 mm, 19.92 mm, 19.93 mm, 19.94 mm, 19.95 mm, 19.96 mm, 19.97 mm, 19.98 mm, 19.99 mm, or 20 mm as measured on the major axis, (ii) a width of approximately 11 mm, 11.01 mm, 11.02 mm, 11.03 mm, 11.04 mm, 11.05 mm, 11.06 mm, 11.07 mm, 11.08 mm, 11.09 mm, 11.1 mm, 11.11 mm, 11.12 mm, 11.13 mm, 11.14 mm, 11.15 mm, 11.16 mm, 11.17 mm, 11.18 mm, 11.19 mm, 11.2 mm, 11.21 mm, 11.22 mm, 11.23 mm, 11.24 mm, 11.25 mm, 11.26 mm, 11.27 mm, 11.28 mm, 11.29 mm, 11.3 mm, 11.31 mm, 11.32 mm, 11.33 mm, 11.34 mm, 11.35 mm, 11.36 mm, 11.37 mm, 11.38 mm, 11.39 mm, 11.4 mm, 11.41 mm, 11.42 mm, 11.43 mm, 11.44 mm, 11.45 mm, 11.46 mm, 11.47 mm, 11.48 mm, 11.49 mm, 11.5 mm, 11.51 mm, 11.52 mm, 11.53 mm, 11.54 mm, 11.55 mm, 11.56 mm, 11.57 mm, 11.58 mm, 11.59 mm, 11.6 mm, 11.61 mm, 11.62 mm, 11.63 mm, 11.64 mm, 11.65 mm, 11.66 mm, 11.67 mm, 11.68 mm, 11.69 mm, 11.7 mm, 11.71 mm, 11.72 mm, 11.73 mm, 11.74 mm, 11.75 mm, 11.76 mm, 11.77 mm, 11.78 mm, 11.79 mm, 11.8 mm, 11.81 mm, 11.82 mm, 11.83 mm, 11.84 mm, 11.85 mm, 11.86 mm, 11.87 mm, 11.88 mm, 11.89 mm, 11.9 mm, 11.91 mm, 11.92 mm, 11.93 mm, 11.94 mm, 11.95 mm, 11.96 mm, 11.97 mm, 11.98 mm, 11.99 mm, 12 mm, 12.01 mm, 12.02 mm, 12.03 mm, 12.04 mm, 12.05 mm, 12.06 mm, 12.07 mm, 12.08 mm, 12.09 mm, 12.1 mm, 12.11 mm, 12.12 mm, 12.13 mm, 12.14 mm, 12.15 mm, 12.16 mm, 12.17 mm, 12.18 mm, 12.19 mm, 12.2 mm, 12.21 mm, 12.22 mm, 12.23 mm, 12.24 mm, 12.25 mm, 12.26 mm, 12.27 mm, 12.28 mm, 12.29 mm, 12.3 mm, 12.31 mm, 12.32 mm, 12.33 mm, 12.34 mm, 12.35 mm, 12.36 mm, 12.37 mm, 12.38 mm, 12.39 mm, 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, 12.5 mm, 12.51 mm, 12.52 mm, 12.53 mm, 12.54 mm, 12.55 mm, 12.56 mm, 12.57 mm, 12.58 mm, 12.59 mm, 12.6 mm, 12.61 mm, 12.62 mm, 12.63 mm, 12.64 mm, 12.65 mm, 12.66 mm, 12.67 mm, 12.68 mm, 12.69 mm, 12.7 mm, 12.71 mm, 12.72 mm, 12.73 mm, 12.74 mm, 12.75 mm, 12.76 mm, 12.77 mm, 12.78 mm, 12.79 mm, 12.8 mm, 12.81 mm, 12.82 mm, 12.83 mm, 12.84 mm, 12.85 mm, 12.86 mm, 12.87 mm, 12.88 mm, 12.89 mm, 12.9 mm, 12.91 mm, 12.92 mm, 12.93 mm, 12.94 mm, 12.95 mm, 12.96 mm, 12.97 mm, 12.98 mm, 12.99 mm, or 13 mm, and (iii) a height or thickness of approximately 5 mm, 5.01 mm, 5.02 mm, 5.03 mm, 5.04 mm, 5.05 mm, 5.06 mm, 5.07 mm, 5.08 mm, 5.09 mm, 5.1 mm,

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5.11 mm, 5.12 mm, 5.13 mm, 5.14 mm, 5.15 mm, 5.16 mm, 5.17 mm, 5.18 mm, 5.19 mm, 5.2 mm, 5.21 mm, 5.22 mm, 5.23 mm, 5.24 mm, 5.25 mm, 5.26 mm, 5.27 mm, 5.28 mm, 5.29 mm, 5.3 mm, 5.31 mm, 5.32 mm, 5.33 mm, 5.34 mm, 5.35 mm, 5.36 mm, 5.37 mm, 5.38 mm, 5.39 mm, 5.4 mm, 5.41 mm, 5.42 mm, 5.43 mm, 5.44 mm, 5.45 mm, 5.46 mm, 5.47 mm, 5.48 mm, 5.49 mm, 5.5 mm, 5.51 mm, 5.52 mm, 5.53 mm, 5.54 mm, 5.55 mm, 5.56 mm, 5.57 mm, 5.58 mm, 5.59 mm, 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, 5.8 mm, 5.81 mm, 5.82 mm, 5.83 mm, 5.84 mm, 5.85 mm, 5.86 mm, 5.87 mm, 5.88 mm, 5.89 mm, 5.9 mm, 5.91 mm, 5.92 mm, 5.93 mm, 5.94 mm, 5.95 mm, 5.96 mm, 5.97 mm, 5.98 mm, 5.99 mm, or 6 mm. In yet another embodiment, the pharmaceutical composition may have (i) a length of approximately 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, or 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, or 19.3 mm as measured on the major axis, (ii) a width of approximately 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, or 12.5 mm, and (iii) a height or thickness of approximately 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, or 5.8 mm.

In another embodiment, the composition may be expandable. That is, the composition has size that is small enough for oral intake, but the composition absorbs water from the gastric fluid and swells to a size that prevents its passage through the pylorus. Such a composition comprises at least one swellable, expandable material, such as a polymer, resin, hydrocolloid, hydrogel, or the like. In various embodiments, the composition may swell to a size that is about 110% to about 200% of the original volume within about 30 minutes of administration. For example, the composition may swell to approximately 115% of its original volume within 30 minutes of administration, and at a later time may swell to a volume that is 130% or more of the original volume. In other embodiments, the composition may exhibit a volume increase of two-fold or more. Additionally, the composition may become slippery upon absorption of water, which provides resistance to peristalsis and further promotes gastric retention. The swellable material degrades or erodes over a specified period of time (e.g., the dosing interval) such that the composition is no longer retained in the stomach. In one embodiment, the ER layer swells upon imbibition of fluid to a size which is about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% larger than the size of the ER layer prior to imbibition of fluid. In another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 25% larger than the size of the ER layer prior to imbibition of fluid within about 15 minutes of the start of fluid imbibition. In still another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 100% larger than the size of the ER layer prior to imbibition of fluid within about 45 min, 50 min, 60 min, 75 min, or 90 min of the start of fluid imbibitions.

In yet another embodiment, the length of the composition increases by about 4%, 4.25%, 4.5%, 4.75%, 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, or 13% within about

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10 minutes of the start of fluid imbibition. In still another embodiment, the length of the composition increases by about 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 15 minutes of the start of fluid imbibition. In yet another embodiment, the length of the composition increases by about 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 20 minutes of the start of fluid imbibition. In a further embodiment, the length of the composition increases by about 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 30 minutes of the start of fluid imbibition. In another embodiment, the length of the composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18% within about 45 minutes of the start of fluid imbibition. In yet another embodiment, the length of the composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, or 19% within about 55 minutes of the start of fluid imbibition. In still another embodiment, the length of the composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, or 19% within about 60 minutes of the start of fluid imbibition.

In a further embodiment, the width of the composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 10 minutes of the start of fluid imbibition. In still another embodiment, the width of the composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 15 minutes of the start of fluid imbibition. In yet another embodiment, the width of the composition increases by about 6%, 6.25%,

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6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 20 minutes of the start of fluid imbibition. In a further embodiment, the width of the composition increases by about 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, or 24% within about 30 minutes of the start of fluid imbibition. In another embodiment, the width of the composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20.0%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 45 minutes of the start of fluid imbibition. In yet another embodiment, the width of the composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20.0%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 55 minutes of the start of fluid imbibition. In still another embodiment, the width of the composition increases by about 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, 25%, 25.25%, 25.5%, 25.75%, or 26% within about 60 minutes of the start of fluid imbibition.

In additional embodiments, the pharmaceutical composition may have (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, or 21 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, or 14 mm within about 5 minutes of the start of fluid imbibition. In other embodiments, the pharmaceutical composition may have (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, or 22 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4

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mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 10 minutes to about 15 minutes of the start of fluid imbibition. In still other embodiments, the pharmaceutical composition may have (i) a length of about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, or 22.5 mm; and (ii) a width of about 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 20 minutes to about 25 minutes of the start of fluid imbibition. In additional embodiments, the pharmaceutical composition may have (i) a length of about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, or 23 mm; and (ii) a width of about 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 30 minutes to about 35 minutes of the start of fluid imbibition. In still other embodiments, the pharmaceutical composition may have (i) a length of about 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2 mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 50 minutes to about 55 minutes of the start of fluid imbibition. In yet another embodiment, the pharmaceutical composition may have (i) a length of about 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2 mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 50 minutes to about 55 minutes of the start of fluid imbibition.

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mm, 15.9 mm, or 16 mm; and (iii) a height of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 60 minutes of the start of fluid imbibition.

In a further embodiment, the composition contains at least one swellable polymer. For example, the composition may include chitosan, methylcellulose, polyvinyl acetate, purified shellac, or an expansive polymeric film, such as one composed of polyvinyl acetate and shellac.

In still another embodiment, the physical property of the composition that imparts gastric retention may be the shape of the composition. For example, the composition may have a ring, tetrahedron, spiral, coil, planar disc, planar multilobe, continuous stick, sheet, oval, parallelogram, or string geometric configuration, wherein the composition is unable to pass through the pyloric sphincter. In some iterations, the composition may be folded into a pharmaceutical carrier (e.g., a gelatin capsule) or secured by readily dissolvable (e.g., gelatin) strips such that, upon dissolution of the carrier or strips, the composition unfolds in the stomach. In general, unfoldable compositions comprise biodegradable polymers such that the composition is degraded and/or reduced in size over a specified period of time (e.g., the dosing interval). In another embodiment, the composition has a diameter of greater than or equal to 7.5 mm.

In yet another embodiment, the physical property of the composition that imparts gastric retention may be the adhesivity of the composition. Bio-mucoadhesive compositions bind to the gastric epithelial cell surface, or mucin, and increase gastric retention time by increasing the intimacy and duration of contact between the composition and the biological membrane. Bio-mucoadhesive compositions generally comprise a natural or synthetic polymer that is capable of adhering to a biological membrane (e.g., a bioadhesive polymer) or the mucus lining of the stomach or intestinal tract (e.g., a mucoadhesive polymer). Certain hydrophilic polymers tend to imbibe large amounts of water and become sticky, thereby acquiring bioadhesive properties. The adhesion of polymers to a mucus or epithelial cell surface may involve various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonding may result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent or non-covalent (e.g., ionic bonds, hydrogen bonds, van der Waals interactions, etc.). Moreover, certain polymers may bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention. For example, certain plant lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

In still another embodiment, the physical property of the composition that imparts gastric retention may be the density of the composition. In one iteration, the composition may have a low density with sufficient buoyancy such that the composition floats over the gastric contents and remains in the stomach for a prolonged period. Floating compositions may be effervescent or non-effervescent. Effervescent compositions generally comprise matrices prepared with swellable polymers and an effervescent component. For example, the effervescent component can be either a carbonate or bicarbonate salt (e.g., sodium bicarbonate, calcium bicarbonate), an organic acid (e.g., citric acid, tartaric acid), or any combination thereof. The effervescent component can also be a floating chamber filled with vacuum, air, an inert gas, or a liquid that gasifies at body temperature. Floatability is generally achieved by generation of gas bubbles. Gas may be introduced into the floating chamber by the volatilization of

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an organic solvent, or by an effervescent reaction between a carbonate-bicarbonate salt and an organic acid. The matrices may be fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified matrix. This maintains the buoyancy of the composition, causing it to float. In another embodiment, the composition may also contain a polymer which exhibits floating characteristics, such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, crospovidone, sodium carboxymethyl cellulose, or ethyl cellulose. In a further embodiment, the composition may comprise a device having a hollow deformable unit that converts from a collapsed to expanded form and vice versa. The unit is supported by a housing that is internally divided into two chambers separated by a pressure-sensitive movable bladder. The first chamber contains the therapeutic agent and the second contains a volatile liquid (e.g., cyclopentane, ether) that vaporizes at body temperature and imparts buoyancy to the system. The system also contains a bioerodible plug to aid in the exit from the body. Further embodiments of this two chamber system are disclosed in U.S. Pat. Nos. 3,901,232 and 3,786,813, which are hereby incorporated by reference. In still a further embodiment, the composition may contain hollow microspheres or microballoons, which cause the composition to float. The composition may also comprise floating micro-particles such as polypropylene foam, Eudragit, ethyl cellulose, or polymethyl methacrylate (PMMA).

Noneffervescent compositions incorporate a high level of one or more gel-forming, highly swellable, cellulosic hydrocolloids. Upon contact with the gastric contents, these hydrocolloids hydrate and forms a colloidal gel barrier, wherein air trapped by the swollen hydrocolloid confers buoyancy to this composition. In another iteration, the composition may have a density that exceeds the density of normal gastric contents such the composition sinks to the bottom of the stomach (i.e., the antrum) where it is entrapped in the folds of the antrum and withstands the peristaltic waves of the gastric wall. In yet another iteration, the composition has a density that is greater than or equal to 1.3 g/mL.

In one embodiment, the composition is retained in the stomach due to the presence of an extended release polymer that absorbs water from the gastric contents and swells or expands to a size that cannot pass through the pyloric sphincter. As a consequence, the opioid and the other API are slowly released from the composition in the stomach and absorbed in the upper gastrointestinal tract.

In still another embodiment, the composition may contain an agent which delays the passage of the composition through the pyloric sphincter. For example, the composition may include triethanol amine myristate or propantheline.

(ii) Opioid Release

Because opioids reduce gastric motility, the erosion time of the dosage form can be increased (thus, hindering drug release) if the opioid is not properly dosed. The gastric retentive extended release composition disclosed herein is engineered to release the opioid(s) at a rate that is sufficient to delay gastric emptying such that the composition is retained in the stomach for a longer period of time than a comparable composition that is not gastric retentive. For example, the composition may be designed to release the opioid(s) at a rate that delays gastric emptying by about 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2.0 hours, 2.5 hours, 3.0 hours, 3.5 hours, 4.0 hours, 4.5 hours, or 5.0 hours. The rate of release of the opioid(s) may be manipulated by selecting a suitable extended release component for inclusion in an extended release portion of the composition. For example, in embodiments in which the extended release component is an

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extended release polymer, the extended release polymer generally is selected such that the composition releases the opioid(s) at a rate that delays gastric emptying by the desired amount. Additionally, the rate of release of the opioid(s) from the composition may be adjusted by selecting the proper ratio of opioid present in the at least one immediate release and the at least one extended release portions of the composition. For instance, the proportion of the opioid(s) in the at least one immediate release portion and the at least one extended release portion may be about 20:80, 21:79, 22:78, 23:77, 24:76, 25:75, 26:74, 27:73, 28:72, 29:71, 30:70, 31:69, 32:68, 33:67, 34:66, 35:65, 36:64, 37:63, 38:62, 39:61, or 40:60.

Additionally, the gastric retentive extended release composition is engineered to release the opioid(s) at a rate that is insufficient to cause any serious adverse gastrointestinal effects. Adverse gastrointestinal effects include, but are not limited to, intestinal hypomotility, intestinal blockage, intestinal pseudo-obstruction, abdominal distention, bloating, constipation, intestinal distress, severe intestinal contractions, colon spasms, hypoactive bowel, and increased anal sphincter tone.

(iii) Overall Composition

With the knowledge of the preferred dissolution and pharmacokinetic profiles for the opioid and the additional API, and the pharmacodynamics effects of the opioid and the additional API, a composition under the present invention can be developed using any of the gastric retentive dosage forms discussed above. Moreover, a composition under the present invention can be developed using another gastric retentive dosage form that achieves the same dissolution, pharmacokinetic, and pharmacodynamic profiles as the compositions disclosed herein. A composition could also be developed that is a sustained release formulation which lacks one of the specific gastric retentive dosage forms discussed above, yet, achieves the same dissolution and pharmacokinetic profiles, and exhibits the pharmacodynamic effects.

(e) Administration of the Gastric Retentive Extended Release Composition

The gastric retentive extended release composition may be administered to a subject in need thereof, wherein the subject may be either in a fed state or a fasted state. In general, a fed state is defined as having consumed food within about 30 min prior to administration of the composition. The food may be a high fat meal, a low fat meal, a high calorie meal, or a low calorie meal. A fasted state may be defined as not having ingested food for at least 10 hours prior to administration of the composition. In some embodiments, the subject may have fasted for at least 10 hours prior to the first dose and refrains from ingesting food for at least one hour prior to administration of subsequent doses. In other embodiments, the fasted subject may not have ingested food for at least 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours prior to administration of each dose of the composition.

Upon oral administration of the composition, the other API(s) in the composition produce a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% under fed and fasted conditions. In various embodiments, the pharmacokinetic parameter may vary by less than about 25%, 20%, 15%, 10%, or 5% under fed and fasted conditions. The pharmacokinetic parameter of the other API(s) that is independent of food may be, but is not limited to, C_{max} , C_{1hr} , C_{2hr} , AUC, partial AUC, T_{max} , and T_{lag} . Additionally, the opioid(s) in the composition produce

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a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% under fed and fasted conditions. In various embodiments, the pharmacokinetic parameter may vary by less than about 25%, 20%, 15%, 10%, or 5% under fed and fasted conditions. In one embodiment, the pharmacokinetic parameter of the opioid that is independent of food may be, but is not limited to, C_{max} , C_{1hr} , C_{2hr} , AUC, partial AUC, T_{max} , and T_{lag} . In a further embodiment, the compositions disclosed herein may be administered to a subject in need thereof without regard to food.

(f) Dosage Forms

The physical form of the pharmaceutical compositions disclosed herein can and will vary. In one embodiment, the composition is provided as a solid dosage form comprising at least one extended release portion and, optionally, at least one immediate release portion. Suitable solid dosage forms include tablets, caplets, capsules, encapsulated beads, and gelcaps. Non-limiting types of tablets include coated tablets, uncoated tablets, bilayer tablets, multi-particle tablets, monolithic tablets, matrix tablets, compressed tablets, and molded tablets. Non-limiting types of capsules include hard capsules and multi-layer capsules.

In one embodiment, the dosage form may be a capsule. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, hard cellulose capsules, and hydrogel capsules. In one example, the core of the capsule may comprise one extended release portion comprising the opioid(s) and other API(s) and the shell of the capsule may comprise one immediate release portion of the composition comprising the opioid(s) and other API(s). In another example, the core of the capsule may comprise two extended release portions, each comprising one of the opioid or the other API, and the shell of the capsule may comprise the immediate release portion of the composition comprising both the opioid and the other API. In still another example, the core of the capsule may comprise one extended release portion, comprising either the opioid or the other API, and the shell of the capsule may comprise the immediate release portion of the composition comprising either the opioid and the other API. In an additional example, the core of the capsule may comprise multiple extended release and immediate release portions, each comprising one of the opioid or the other API. In still another embodiment, the dosage form may be a sustained release capsule comprising the opioid or the other API and exhibiting immediate release and/or extended release properties.

In another embodiment, the dosage form may be a tablet comprising at least one extended release portion and at least one immediate release portion. The at least one immediate release portion may be adjacent to, abutting, or surrounding the at least one extended release portion. In one embodiment, the dosage form may be a bilayer tablet comprising one extended release portion comprising both the opioid and the other API and one immediate release portion comprising both the opioid and the other API. In still another embodiment, the dosage form may be a sustained release tablet comprising the opioid and/or the other API and exhibiting immediate release and/or extended release properties. The bilayer tablet may comprise a coating.

In another embodiment, the dosage form may be a multi-layer tablet comprising two extended release portions, each

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comprising one of the opioid or the other API, and one immediate release portion comprising both the opioid and the other API. In yet another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the opioid or the other API, and two immediate release portions, each comprising one of the opioid or the other API. In a further embodiment, the dosage form may be a multilayer tablet comprising multiple extended release portions, each comprising one of the opioid, the other API, or both, and one immediate release portion comprising both the opioid and the other API. In yet another embodiment, the dosage form may be a multilayer tablet comprising multiple extended release portions, each comprising one of the opioid, the other API, or both, and multiple immediate release portions comprising the opioid, the other API, or both. In still another embodiment, the dosage form may be a sustained release tablet comprising the opioid. In yet another embodiment, the immediate release portion may be part of or homogeneously mixed with the extended release portion.

In certain embodiment, the tablet may have a friability of no greater than about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.7% or 1.0%. In another embodiment, the tablet may have a friability of greater than 0 but less than about 1.0%, greater than 0 but less than about 0.5%, greater than 0 but less than about 0.3%, or greater than 0 but less than about 0.2%. In still another embodiment, the tablet may have a friability of zero.

In one embodiment, the tablet may have a hardness of at least about 10 Kilopond (also known as kilopons) (kp). In some embodiments, the tablet may have a hardness of about 9 kp to about 25 kp, or about 12 kp to about 20 kp. In further embodiments, the tablet may have a hardness of about 11 kp, 12 kp, 13 kp, 14 kp, 15 kp, or 16 kp.

In additional embodiments, the tablet may have a content uniformity of from about 85 to about 115 percent by weight or from about 90 to about 110 percent by weight, or from about 95 to about 105 percent by weight. In other embodiments, the content uniformity may have a relative standard deviation (RSD) equal to or less than about 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1.0%, or 0.5%.

(g) Abuse and Tamper Resistant Properties of the Composition

Extended release pain medications have provided many benefits to patients in the management of their chronic pain by providing a sustained release over time of a larger quantity of drug than is typically contained in an immediate release formulation. Consequently, these dosage forms (especially if they contain opioids) are attractive targets for drug abusers looking to defeat the extended release formulation to allow immediate bolus administration or "dose-dumping" of the entire drug contents of the dosage form.

Dosage forms of the pharmaceutical composition disclosed herein may be more resistant to crushing, grinding, pulverizing, or other common means used to produce a powder than an immediate release product. Accordingly, some embodiment forms are tamper resistant and less prone to abuse or misuse. For example, certain embodiments may not be crushed into a powder and snorted. Additionally, some embodiments comprising an extended release polymer may not be crushed, mixed with an aqueous solution, and injected (i.e., the resultant mixture becomes extremely viscous and cannot be effectively drawn into a syringe.)

For example, dosage forms of the pharmaceutical composition disclosed herein form a pasty semi-solid mixture when

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dissolved. Thus, the pharmaceutical composition is difficult to draw into a syringe and inject intravenously. The yield of active pharmaceutical ingredient(s) obtained from the pharmaceutical composition is also low (less than 20%).

Further, dosage forms of the pharmaceutical composition disclosed herein cannot easily be snorted. In order for a drug abuser to successfully snort a drug obtained from a dosage form, he must prepare a crushed, finely divided powder form of the dosage form for insufflating the powder into the nasal cavity. However, the pharmaceutical compositions disclosed herein form a clumpy, solid mass and do not allow acceptable absorption through the nasal tissue.

Dosage forms of the pharmaceutical composition disclosed herein also do not allow "dose dumping" caused by the deliberate introduction of alcohol into a drug abuser's stomach which accelerates the release of active ingredient(s) from the time-release formulation. The pharmaceutical compositions disclosed herein are resistant to the accelerated release of active ingredient(s).

In addition, dosage forms of the pharmaceutical composition disclosed herein do not allow for "free basing." Successful free basing by a drug abuser requires the generation of a salt free form of the active pharmaceutical ingredient(s). This requires physical and chemical manipulation to release the active pharmaceutical ingredient(s) from its salt(s) and selective extraction from other matrix excipients. The pharmaceutical composition disclosed herein cannot be easily manipulated to generate a free base preparation.

Moreover, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the average molecular weight of the extended release polymer used in the pharmaceutical composition. In another embodiment, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the amount of the extended release polymer used in the pharmaceutical composition.

In further embodiments, the solid oral dosage forms of the pharmaceutical compositions disclosed herein exhibit substantial differences in the release profiles of oxycodone and acetaminophen when the dosage forms are crushed or ground. Indeed, the intact solid oral dosage forms surprisingly exhibit a higher release rate of both active ingredients than one that is crushed or ground. This suggests that upon grinding or crushing the solid oral dosage forms disclosed herein, the oxycodone and acetaminophen in the immediate release portion are incorporated into the extended release portion, and the pharmaceutical composition loses its immediate release characteristics. This feature may effectively negate a drug abuser's purpose for crushing the solid oral dosage form in the first place—to obtain an early onset of analgesia. Thus, this is an unexpected tamper resistant property of the pharmaceutical compositions disclosed herein.

In another embodiment, as the amount of oxycodone in the pharmaceutical composition increases, so does the duration of gastric retention after administration to a subject. Consequently, if a subject either intentionally or accidentally ingests a larger dose of the pharmaceutical composition than prescribed, the pharmaceutical composition will be retained in the stomach for a longer time period than an IR or traditional ER pharmaceutical composition, thereby giving a medical provider additional time to perform gastric lavage, induce vomiting, or administer activated charcoal to prevent the body from absorbing the oxycodone. In a further embodiment, the pharmaceutical composition provides a medical provider with about an additional 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 2.0 hours, 2.25 hours, 2.5 hours, 2.75 hours, 3.0 hours, 3.25

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hours, 3.5 hours, 3.75 hours, or 4 hours in which to prevent the absorption of oxycodone in the subject. In another embodiment, the pharmaceutical composition provides a medical provider with sufficient time to treat a subject who has overdosed on oxycodone so that death, difficulty breathing, cardiac arrest, and limp muscles do not occur in the subject.

In yet another embodiment, if vomiting is induced or naturally occurs as a result of an increased dose of oxycodone, the entire pharmaceutical composition is expelled from the subject. Thus, toxic concentrations of the oxycodone due to absorption into the subject's blood are prevented by removing the further release of oxycodone. In still another embodiment, if vomiting is induced or naturally occurs as a result of the increased dose of oxycodone about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the pharmaceutical composition is expelled from the subject. In yet another embodiment, if vomiting is induced or naturally occurs within about 30 minutes to about 60 minutes after ingestion of the increased dose of oxycodone about 50% to about 65% of the oxycodone dose is expelled from the subject.

(h) Exemplary Compositions

In one embodiment, the opioid of the gastric retentive extended release composition is oxycodone and the other API is acetaminophen. In another embodiment, the at least one immediate release portion of the composition comprises oxycodone, acetaminophen, or a combination thereof, and the at least one extended release portion of the composition comprises an extended release component and oxycodone, acetaminophen, or a combination thereof. In yet another embodiment, the gastric retentive extended release composition comprises an immediate release portion comprising oxycodone and acetaminophen and an extended release portion comprising oxycodone, acetaminophen and an extended release component. In still yet another embodiment, the compositions comprises two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and an immediate release portion comprising oxycodone and acetaminophen. In another embodiment, the composition comprises two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and two immediate release portions, each comprising one of oxycodone or acetaminophen. In one embodiment, the extended release component comprise at least one extended release polymer. In one exemplary embodiment, the at least one extended release polymer comprises a polyethylene oxide. The molecular weight of the polyethylene oxide may be from about 500,000 Daltons to about 10,000,000 Daltons.

In another embodiment, the composition may comprise from about 5 mg to about 30 mg of oxycodone and from about 250 mg to about 1300 mg of acetaminophen. In one embodiment, the composition may comprise about 15 mg of oxycodone and about 650 mg of acetaminophen. In another embodiment, the composition may comprise about 15 mg of oxycodone and about 500 mg of acetaminophen. In a further embodiment, the composition may comprise about 30 mg of oxycodone and about 500 mg of acetaminophen. In still another embodiment, the composition may comprise about 15 mg of oxycodone and about 325 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of

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oxycodone and about 325 mg of acetaminophen. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of oxycodone and about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 30 mg of oxycodone and about 650 mg of acetaminophen.

In another embodiment, the composition may comprise from about 5 mg to about 30 mg of hydrocodone and from about 250 mg to about 1300 mg of acetaminophen. In one embodiment, the composition may comprise about 15 mg of hydrocodone and about 650 mg of acetaminophen. In another embodiment, the composition may comprise about 15 mg of hydrocodone and about 500 mg of acetaminophen. In a further embodiment, the composition may comprise about 30 mg of hydrocodone and about 500 mg of acetaminophen. In still another embodiment, the composition may comprise about 15 mg of hydrocodone and about 325 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 7.5 mg of hydrocodone and about 325 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of hydrocodone and about 325 mg of acetaminophen. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of hydrocodone and about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 30 mg of hydrocodone and about 650 mg of acetaminophen.

In another embodiment, the composition may comprise from about 5 mg to about 30 mg of opioid and from about 250 mg to about 1300 mg of at least one other API. In one embodiment, the composition may comprise about 15 mg of opioid and about 650 mg of at least one other API. In another embodiment, the composition may comprise about 15 mg of opioid and about 500 mg of at least one other API. In a further embodiment, the composition may comprise about 30 mg of opioid and about 500 mg of at least one other API. In still another embodiment, the composition may comprise about 15 mg of opioid and about 325 mg of at least one other API. In yet another exemplary embodiment, the composition may comprise about 7.5 mg of opioid and about 325 mg of at least one other API. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of opioid and about 325 mg of at least one other API. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of opioid and about 650 mg of at least one other API. In another exemplary embodiment, the composition may comprise about 30 mg of opioid and about 650 mg of at least one other API. In yet another exemplary embodiment, the composition may comprise about 22.5 mg of opioid and about 925 mg of at least one other API.

In a further embodiment, a single dosage form of the pharmaceutical composition disclosed herein (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as either two dosage forms (e.g., two tablets) of the composition formulated at half the strength, or three dosage forms (e.g., three tablets) of the composition formulated at a third of the strength. In yet another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen). In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single

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dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 5 mg of oxycodone and about 216.7 mg of acetaminophen). In yet another embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet comprising 22.5 mg of oxycodone and 650 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet configuration totaling 30 mg of oxycodone and 650 mg of acetaminophen. In yet a further exemplary embodiment, a pharmaceutical composition comprising 21 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 10.5 mg of oxycodone and 325 mg of acetaminophen). In yet another exemplary embodiment, a pharmaceutical composition comprising 22.5 mg of oxycodone and 925 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen).

In a further embodiment, a single dosage form of the pharmaceutical composition disclosed herein (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as either two dosage forms (e.g., two tablets) of the composition formulated at half the strength, or three dosage forms (e.g., three tablets) of the composition formulated at a third of the strength. In yet another exemplary embodiment, the pharmaceutical composition comprising 15 mg of hydrocodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 7.5 mg of hydrocodone and 325 mg of acetaminophen). In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of hydrocodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 5 mg of hydrocodone and about 216.7 mg of acetaminophen). In yet another embodiment, the pharmaceutical composition comprising 15 mg of hydrocodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 7.5 mg of hydrocodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet comprising 22.5 mg of hydrocodone and 650 mg

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of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of hydrocodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 15 mg of hydrocodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet configuration totaling 30 mg of hydrocodone and 650 mg of acetaminophen. In yet a further exemplary embodiment, a pharmaceutical composition comprising 21 mg of hydrocodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 10.5 mg of hydrocodone and 325 mg of acetaminophen). In yet another exemplary embodiment, a pharmaceutical composition comprising 22.5 mg of hydrocodone and 925 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 7.5 mg of hydrocodone and 325 mg of acetaminophen).

In another embodiment, the at least one immediate release portion may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the composition and from about 20% to about 30% (w/w) of the total amount of oxycodone present in the composition, whereas the at least one extended release portion may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the composition and from about 70% to about 80% (w/w) of the total amount of oxycodone present in the composition. In an exemplary embodiment, the at least one immediate release portion may comprise about 50% of the total amount of acetaminophen and about 25% (w/w) of the total amount of oxycodone present in the composition, and the at least one extended release portion may comprise about 50% of the total amount of acetaminophen and about 75% (w/w) of the total amount of oxycodone present in the composition.

In yet another embodiment, an immediate release portion of the composition may comprise, by weight of such immediate release portion, from about 70% to about 80% acetaminophen and from about 0.5% to about 1% of oxycodone, and an extended release portion of the composition may comprise, by weight of such extended release portion, from about 30% to about 50% of the extended release polymer, from about 20% to about 40% of acetaminophen, and from about 0.5% to about 2% of oxycodone.

In another embodiment, the composition may comprise from about 7.5 mg to about 30 mg of oxycodone and from about 325 mg to about 650 mg of acetaminophen, wherein the at least one immediate release portion may comprise about 25% of the total amount of oxycodone and about 50% of the total amount of acetaminophen present in the composition, and the at least one extended release portion may comprise about 75% of the total amount of oxycodone and about 50% of the total amount of acetaminophen present in the composition, and each extended release portion further comprises from about 35% to about 45%, by weight of each extended release portion, of an extended release polymer comprising a polyethylene oxide. Other exemplary formulations are set forth in Charts 1-3 below.

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CHART 1

		Representative hydrocodone formulations.*									
		Formulation No.									
		1	2	3	4	5	6	7	8	9	10
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Hydrocodone bitartrate	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
Extended Release Layer	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Hydrocodone bitartrate	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N12K	292.8	—	—	—	287.7	—	—	321.8	155.5	—
	Polyox 303	—	—	244.2	—	—	—	275.5	—	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
		Formulation No.									
		11	12	13	14	15	16	17	18	19	20
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Hydrocodone bitartrate	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
Extended Release Layer	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Hydrocodone bitartrate	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N12K	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox 303	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
		Formulation No.									
		21	22	23	24	25	26	27	28	29	30
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Hydrocodone bitartrate	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—

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CHART 1-continued

Representative hydrocodone formulations.*											
Extended Release Layer	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Hydrocodone bitartrate	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N60K	292.8	—	—	—	287.7	—	—	321.8	155.5	—
	Polyox 205	—	—	244.2	—	—	—	275.5	—	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		31	32	33	34	35	36	37	38	39	40
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Hydrocodone bitartrate	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
Extended Release Layer	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Hydrocodone bitartrate	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N60K	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox 205	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
Formulation No.											
		41	42	43	44	45	46	47	48	49	50
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Hydrocodone bitartrate	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
Extended Release Layer	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Hydrocodone bitartrate	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	.045	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125

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CHART 1-continued

Representative hydrocodone formulations.*											
	dihydrate										
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox 1105	262.2	—	—	—	301.6	—	—	250.3	188.3	—
	Polyox N-750	—	—	244.2	—	—	—	275.5	—	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		51	52	53	54	55	56	57	58	59	60
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Hydrocodone bitartrate	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Hydrocodone bitartrate	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox 1105	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox N-750	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
Formulation No.											
		61	62	63	64	65	66	67	68	69	70
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Hydrocodone bitartrate	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
Extended Release Layer	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Hydrocodone bitartrate	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox 301	292.8	—	—	—	287.7	—	—	321.8	155.5	—
	Polyox N-80	—	—	244.2	—	—	—	275.5	—	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3

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CHART 1-continued

		Representative hydrocodone formulations.*									
		Formulation No.									
		71	72	73	74	75	76	77	78	79	80
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Hydrocodone bitartrate	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Hydrocodone bitartrate	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox 301	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox N-80	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2

*All weights in mg.

CHART 2

		Representative oxycodone formulations.*									
		Formulation No.									
		81	82	83	84	85	86	87	88	89	90
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
Extended Release Layer	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—

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CHART 2-continued

Representative oxycodone formulations.*											
	cellulose										
	Polyox N12K	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 1105	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		91	92	93	94	95	96	97	98	99	100
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N12K	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox 1105	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
Formulation No.											
		101	102	103	104	105	106	107	108	109	110
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30

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CHART 2-continued

Representative oxycodone formulations.*											
Extended Release Layer	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N60K	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 205	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		111	112	113	114	115	116	117	118	119	120
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N60K	—	45.5	249.9	24.3	282.0	49.8	200.1	240.1	186.8	—
	Polyox 205	268.4	—	53.6	70.2	—	—	36.3	10.4	—	259.3
	Hydroxypropyl methyl cellulose	—	90.5	—	65.4	—	192.1	—	—	127.3	142.0
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
Formulation No.											
		121	122	123	124	125	126	127	128	129	130
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0

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CHART 2-continued

Representative oxycodone formulations.*											
Extended Release Layer	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N-750	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 301	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		131	132	133	134	135	136	137	138	139	140
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.5
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N-750	63.4	30.1	125.9	100.3	149.2	63.2	150.5	140.3	94.3	—
	Polyox 301	210.4	—	175.8	60.7	175.8	—	160.5	149.7	100.8	194.6

		Additional opioid formulations.*								
		Formulation No.								
		141	142	143	144	145	146	147	148	
Immediate Release Layer	APAP	250.0	250.0	250.0	250.0	250.0	250.0	325.0	325.0	
	Oxycodone hydrochloride	3.75	3.75	3.75	7.5	7.5	7.5	3.75	—	
	Hydrocodone bitartrate	—	—	—	—	—	—	—	3.75	
	Microcrystalline cellulose	23.72	23.72	23.72	32.42	32.42	32.42	28.10	28.1	
	Pregelatinized starch	0.50	0.50	0.50	1.00	1.00	1.00	0.50	0.50	
	Citric Acid Anhydrous	0.25	0.25	0.25	0.50	0.50	0.50	0.25	0.25	
	EDTA disodium salt, dihydrate	0.05	0.05	0.05	0.10	0.10	0.10	0.05	0.05	
	Hydroxypropyl cellulose	25.23	25.23	25.23	26.43	26.43	26.43	32.24	32.24	
	Croscarmellose sodium	19.21	19.21	19.21	20.13	20.13	20.13	12.09	25.09	
	Silicon dioxide	1.63	1.63	1.63	1.70	1.70	1.70	2.09	2.09	
Extended Release Layer	Magnesium stearate	0.81	0.81	0.81	0.85	0.85	0.85	1.045	1.045	
	APAP	250.0	250.0	250.0	250.0	250.0	250.0	325.0	325.0	
	Hydrocodone bitartrate	—	—	—	—	—	—	—	11.25	
	Oxycodone hydrochloride	11.25	11.25	11.25	22.5	22.5	22.5	11.25	—	
	Microcrystalline cellulose	175.24	103.74	103.74	159.62	88.12	88.12	23.85	95.19	
	Pregelatinized starch	1.50	1.50	1.50	3.00	3.00	3.00	1.5	1.5	
	Citric Acid Anhydrous	0.75	0.75	0.75	1.50	1.50	1.50	0.75	0.75	
	EDTA disodium salt, dihydrate	0.15	0.15	0.15	0.30	0.30	0.30	0.15	0.15	
	Hydroxypropyl cellulose	15.13	15.13	15.13	17.11	17.11	17.11	—	19.16	
	Polyox 1105	250.25	321.75	—	250.25	321.75	—	321.02	249.68	
	Polyox N60K	—	—	321.75	—	—	321.75	—	—	
	Silicon Dioxide	3.58	3.58	3.58	3.58	3.58	3.58	3.57	3.57	
	Magnesium Stearate	7.15	7.15	7.15	7.15	7.15	7.15	7.13	7.13	
			Formulation No.							
			149	150	151	152	153	154	155	
	Immediate Release Layer	APAP	325.0	325.0	325.0	325.0	325	325	325	—
		Oxycodone hydrochloride	—	—	—	3.75	—	—	3.75	—
		Hydrocodone bitartrate	3.75	3.75	—	3.75	3.75	—	—	3.75
		Microcrystalline cellulose	28.1	28.1	28.10	28.10	28.10	28.10	28.10	28.10
		Pregelatinized starch	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Citric Acid Anhydrous		0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	
EDTA disodium salt, dihydrate		0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	
Hydroxypropyl cellulose		32.24	32.24	32.23	32.23	32.24	32.24	32.24	32.24	
Croscarmellose sodium		25.09	25.09	25.087	25.087	25.09	25.09	25.09	25.09	
Silicon dioxide		2.09	2.09	2.09	2.09	2.09	2.09	2.09	2.09	
Extended Release Layer	Magnesium stearate	1.045	1.045	1.045	1.045	1.05	1.05	1.05	1.05	
	APAP	325.0	325.0	325.0	325.0	325	325	325	—	
	Hydrocodone bitartrate	11.25	11.25	—	11.25	11.25	—	—	11.25	
	Oxycodone hydrochloride	—	—	11.25	—	—	11.25	—	—	
	Microcrystalline cellulose	23.85	23.85	23.85	23.85	95.19	95.19	23.85	—	
	Pregelatinized starch	1.5	1.5	1.50	1.50	1.50	1.50	1.50	1.50	
	Citric Acid Anhydrous	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	
	EDTA disodium salt, dihydrate	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	
	Hydroxypropyl cellulose	19.16	19.16	19.16	19.16	19.16	19.16	19.16	19.16	
	Polyox 1105	321.02	—	321.02	321.02	249.68	249.68	—	—	
	Polyox N12K	—	—	—	—	—	—	—	321.02	
	Polyox N60K	—	321.02	—	—	—	—	—	—	
	Silicon Dioxide	3.57	3.57	3.57	3.57	3.57	3.57	3.57	3.57	
	Magnesium Stearate	7.13	7.13	7.13	7.13	7.13	7.13	7.13	7.13	

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CHART 3-continued

		Additional opioid formulations.*						
		Formulation No.						
		156	157	158	159	160	161	162
Immediate Release Layer	APAP	325	325	325.0	325.0	325.0	162.5	162.5
	Oxycodone hydrochloride	—	3.75	—	3.75	3.75	2.5	3.75
	Hydrocodone bitartrate	3.75	—	3.75	—	—	—	—
	Microcrystalline cellulose	28.10	28.10	28.1	28.1	28.10	15.50	18.40
	Pregelatinized starch	0.50	0.50	0.50	0.50	0.50	0.33	0.50
	Citric Acid Anhydrous	0.25	0.25	0.25	0.25	0.25	0.17	0.25
	EDTA disodium salt, dihydrate	0.05	0.05	0.05	0.05	0.05	0.033	0.05
	Hydroxypropyl cellulose	32.24	32.24	32.24	32.24	32.23	16.32	16.72
	Croscarmellose sodium	25.09	25.09	25.09	25.09	25.087	12.70	13.01
	Silicon dioxide	2.09	2.09	2.09	2.09	2.09	1.06	1.08
	Magnesium stearate	1.05	1.05	1.045	1.045	1.045	0.53	0.54
	APAP	325	325	325.0	325.0	325.0	162.5	162.5
	Hydrocodone bitartrate	11.25	—	11.25	11.25	—	—	—
	Oxycodone hydrochloride	—	11.25	—	—	11.25	7.5	11.25
Extended Release Layer	Microcrystalline cellulose	23.85	23.85	23.85	23.85	23.85	201.02	195.80
	Pregelatinized starch	1.50	1.50	1.5	1.5	1.50	1.00	1.50
	Citric Acid Anhydrous	0.75	0.75	0.75	0.75	0.75	0.50	0.75
	EDTA disodium salt, dihydrate	0.15	0.15	0.15	0.15	0.15	0.10	0.15
	Hydroxypropyl cellulose	19.16	19.16	19.16	19.16	19.16	9.91	10.57
	Polyox 1105	321.02	—	—	—	—	321.75	321.75
	Polyox N12K	—	321.02	—	—	321.02	—	—
	Polyox N60K	—	—	321.02	321.02	—	—	—
	Silicon Dioxide	3.57	3.57	3.57	3.57	3.57	3.58	3.58
	Magnesium Stearate	7.13	7.13	7.13	7.13	7.13	7.15	7.15

*All weights in mg.

(i) In Vitro Release Properties of the Exemplary Compositions

In one embodiment, the composition comprises at least one immediate release portion and at least one extended release portion, each of which comprise either oxycodone or hydrocodone, acetaminophen, or a combination thereof. The in vitro release rates of oxycodone, hydrocodone, and acetaminophen may be measured in 900 mL of 0.1 N HCl using a USP type II paddle apparatus and at paddle speed of either about 100 rpm or about 150 rpm and at a constant temperature of 37° C.

In one embodiment, the at least one immediate release portion of the composition may have in vitro release rate of oxycodone and acetaminophen as follows: more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion is released in about 15 minutes, or essentially 100% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes. In another embodiment, more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 min. In yet another embodiment, essentially 100% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 min.

In one embodiment, the at least one extended release portion of the composition may have in vitro release rates of oxycodone as follows: from about 1% to about 20% of the oxycodone present in the at least one extended release portion may be released within about 15 min, from about 35% to about 60% of the oxycodone present in the at least one extended release portion is released within about 2 hours, from about 60% to about 90% of the oxycodone present in the at least one extended release portion is released in about 4 hours, and at least about 90% of the oxycodone present in the at least one extended release portion is released within about 8 hours.

In still another embodiment, the at least one extended release portion may have in vitro release rates of oxycodone as follows: from about 1% to about 20% of the oxycodone present in the extended release portion may be released within about 15 min, from about 35% to about 60% of the oxycodone present in the extended release portion may be released within about 2 hours, from about 60% to about 90% of the oxycodone present in the extended release portion may be released within about 4 hours, and from about 90% to about 100% of the oxycodone present in the extended release portion may be released within about 8 hours.

In yet another embodiment, the at least one extended release portion may have in vitro release rates of oxycodone as follows: from about 1% to about 10% of the oxycodone present in the extended release portion may be released within about 15 min, from about 40% to about 50% of the oxycodone present in the extended release portion may be released within about 2 hours, from about 70% to about 80% of the oxycodone present in the extended release portion may be released within about 4 hours, and from about 90% to about 100% of the oxycodone present in the extended release portion may be released within about 8 hours.

In one embodiment, the at least one extended release portion of the composition may have in vitro release rates of acetaminophen as follows: from about 1% to about 15% of the acetaminophen present in the at least one extended release portion may be released within about 15 min, from about 20% to about 50% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 35% to about 75% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 65% to about 100% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

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In another embodiment, the at least one extended release portion of the composition may have in vitro release rates of acetaminophen as follows: from about 1% to about 15% of the acetaminophen present in the at least one extended release portion may be released within about 15 min, from about 20% to about 50% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 35% to about 75% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 65% to about 100% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

In one embodiment, the in vitro release rates of oxycodone from the composition may be as follows: about 20% to about 45% of oxycodone may be released from the composition within about 15 minutes, from about 50% to about 75% of oxycodone may be released from the composition in about 2 hours, from about 70% to about 95% of oxycodone may be released from the composition within about 4 hours, and from about 90% to about 100% of oxycodone may be released from the composition within about 8 hours.

In another embodiment, the in vitro release rates of oxycodone from the composition may be as follows: about 20% to about 45% of oxycodone may be released from the pharmaceutical composition within about 15 minutes, from about 50% to about 75% of oxycodone may be released from the pharmaceutical composition within about 2 hours, from about 70% to about 95% of oxycodone may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 100% of oxycodone may be released from the pharmaceutical composition within about 8 hours.

In one embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: from about 40% to about 65% of acetaminophen may be released from the composition in about 15 minutes, from about 55% to about 80% of acetaminophen may be released from the composition in about 2 hours, from about 65% to about 95% of acetaminophen may be released from the composition in about 4 hours, and from about 80% to about 100% of acetaminophen may be released from the composition in about 8 hours.

In another embodiment, the in vitro release rates of acetaminophen from the pharmaceutical composition disclosed herein may be as follows: from about 40% to about 65% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes, from about 55% to about 80% of acetaminophen may be released from the pharmaceutical composition within about 2 hours, from about 65% to about 95% of acetaminophen may be released from the pharmaceutical composition within about 4 hours, and from about 80% to about 100% of acetaminophen may be released from the pharmaceutical composition within about 8 hours. In another embodiment, about 90% to about 100% of the IR dose of acetaminophen is released within about 15 minutes, 30 minutes, 45 minutes or 60 minutes after oral administration. In one embodiment, the dosage form provides a dissolution profile wherein about 20% to about 65%, about 35% to about 55% or about 40% to about 50% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration. In yet another embodiment, the dosage form provides a dissolution profile wherein about 50% to about 95% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration. In another embodiment, the dosage form provides a dissolution profile wherein about 15% to about 40% of the ER dose of acetaminophen is released from the ER layer between

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about 1 and 2 hours after administration. In one embodiment, not more than 50% of the ER dose of acetaminophen is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the ER dose of acetaminophen is released within about the first hour. In another embodiment, not more than 85% of the ER dose of acetaminophen is released within about 4 hours. In yet another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 55% is released after about 6 hours. In one embodiment, the ER dose of acetaminophen is released over a time period of about 6 to 12, about 8 to 10, or about 9 to 10 hours in vitro. In another embodiment, the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In one embodiment, at least 80% or 85% of the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In another embodiment, at least 90% or 95% of the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro.

In one embodiment, the at least one immediate release portion of the composition may have in vitro release rate of hydrocodone and acetaminophen as follows: more than about 90% of the hydrocodone and/or the acetaminophen present in the at least one immediate release portion is released in about 15 minutes, or essentially 100% of the hydrocodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes. In another embodiment, more than about 90% of the hydrocodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 min. In yet another embodiment, essentially 100% of the hydrocodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 min.

In one embodiment, the at least one extended release portion of the composition may have in vitro release rates of hydrocodone as follows: from about 1% to about 20% of the hydrocodone present in the at least one extended release portion may be released within about 15 min, from about 30% to about 50% of the hydrocodone present in the at least one extended release portion is released within about 2 hours, from about 50% to about 75% of the hydrocodone present in the at least one extended release portion is released in about 4 hours, at least about 80% of the hydrocodone present in the at least one extended release portion is released within about 8 hours, and at least about 90% of the hydrocodone present in the at least one extended release portion is released within about 12 hours.

In yet another embodiment, the at least one extended release portion may have in vitro release rates of hydrocodone as follows: from about 1% to about 20% of the hydrocodone present in the extended release portion may be released within about 15 min, from about 30% to about 50% of the hydrocodone present in the extended release portion may be released within about 2 hours, from about 50% to about 75% of the hydrocodone present in the extended release portion may be released within about 4 hours, and from about 80% to about 100% of the hydrocodone present in the extended release portion may be released within about 8 hours.

In one embodiment, the in vitro release rates of hydrocodone from the composition may be as follows: about 20% to about 50% of hydrocodone may be released from the composition within about 15 minutes, from about 25% to about 55% of hydrocodone may be released from the composition within about 30 minutes, from about 35% to about 65% of

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hydrocodone may be released within about 1 hour, from about 40% to about 80% of hydrocodone may be released from the composition in about 2 hours, from about 60% to about 100% of hydrocodone may be released from the composition within about 4 hours, from about 70% to about 100% of hydrocodone may be released from the composition within about 6 hours, from about 80% to about 100% of hydrocodone may be released from the composition within about 8 hours, from about 90% to about 100% of hydrocodone may be released from the composition within about 12 hours, and from about 90% to about 100% of hydrocodone may be released from the composition within about 18 hours.

In another embodiment, the in vitro release rates of hydrocodone from the composition may be as follows: about 20% to about 40% of hydrocodone may be released from the composition within about 15 minutes, from about 25% to about 45% of hydrocodone may be released from the composition within about 30 minutes, from about 35% to about 55% of hydrocodone may be released within about 1 hour, from about 45% to about 65% of hydrocodone may be released from the composition in about 2 hours, from about 60% to about 85% of hydrocodone may be released from the composition within about 4 hours, from about 70% to about 100% of hydrocodone may be released from the composition within about 6 hours, from about 80% to about 100% of hydrocodone may be released from the composition within about 8 hours, from about 85% to about 100% of hydrocodone may be released from the composition within about 12 hours, and from about 90% to about 100% of hydrocodone may be released from the composition within about 18 hours.

In another embodiment, the in vitro release rates of hydrocodone from the composition may be as follows: about 30% to about 35% of hydrocodone may be released from the composition within about 15 minutes, from about 35% to about 40% of hydrocodone may be released from the composition within about 30 minutes, from about 40% to about 50% of hydrocodone may be released within about 1 hour, from about 50% to about 60% of hydrocodone may be released from the composition in about 2 hours, from about 65% to about 75% of hydrocodone may be released from the composition within about 4 hours, from about 80% to about 90% of hydrocodone may be released from the composition within about 6 hours, from about 90% to about 100% of hydrocodone may be released from the composition within about 8 hours, and from about 95% to about 100% of hydrocodone may be released from the composition within about 12 hours.

In one embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: about 40% to about 65% of acetaminophen may be released from the composition within about 15 minutes, from about 45% to about 65% of acetaminophen may be released from the composition within about 30 minutes, from about 50% to about 70% of acetaminophen may be released from the composition within about 1 hour, from about 55% to about 80% of acetaminophen may be released from the composition within about 2 hours, from about 65% to about 95% of acetaminophen may be released from the composition within about 4 hours, from about 75% to about 100% of acetaminophen may be released from the composition within about 6 hours, from about 80% to about 100% of acetaminophen may be released from the composition within about 8 hours, from about 85% to about 100% of acetaminophen may be released from the composition within about 12 hours, and from about 90% to about 100% of acetaminophen may be released from the composition within about 18 hours.

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In a further embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: about 50% to about 55% of acetaminophen may be released from the composition within about 15 minutes, from about 52% to about 58% of acetaminophen may be released from the composition within about 30 minutes, from about 55% to about 60% of acetaminophen may be released from the composition within about 1 hour, from about 60% to about 65% of acetaminophen may be released from the composition within about 2 hours, from about 70% to about 75% of acetaminophen may be released from the composition within about 4 hours, from about 80% to about 85% of acetaminophen may be released from the composition within about 6 hours, from about 90% to about 95% of acetaminophen may be released from the composition within about 8 hours, and from about 95% to about 100% of acetaminophen may be released from the composition within about 12 hours.

Additionally, the in vitro release rates of oxycodone and acetaminophen from the composition generally are not affected by low concentrations of ethanol (i.e., from about 5% v/v to about 20% v/v) when measured in 900 mL of 0.1N HCl containing the desired percentage of ethanol using a USP type II paddle apparatus and at a constant temperature of 37° C. and about 150 rpm. For example, from about 25% to about 35% of oxycodone and about 50% to about 55% of acetaminophen may be released from the composition within about 15 minutes when measured in the presence of 5% to 20% ethanol, and from about 50% to about 65% of oxycodone and from about 60% to about 70% of acetaminophen may be released from the composition within about 2 hours when measured in the presence of 5% to 20% ethanol.

The in vitro release rates of oxycodone and acetaminophen from the composition generally are reduced, however, in the presence of 40% ethanol. For example, from about 5% to about 15% of the oxycodone and from about 15% to about 25% of the acetaminophen may be released from the composition within about 15 minutes when measured in the presence of 40% ethanol, and from about 35% to about 45% of oxycodone and from about 45% to about 55% of acetaminophen may be released from the composition within about 2 hours when measured in the presence of 40% ethanol.

Stated another way, less oxycodone is extracted from the composition by a solution of 0.1 N HCl and 40% ethanol than is extracted by a solution of 0.1 N HCl. In some embodiments, less than about 75% of the oxycodone that is released in the presence of 0.1N HCl is released in the presence 0.1N HCl containing 40% ethanol. In additional embodiments, less than about 70%, 65%, 60%, 55%, 50%, 45%, or 40% of the oxycodone that may be released in the presence of 0.1N HCl is released in the presence 0.1N HCl and 40% ethanol. For example, less than about 40% of the oxycodone that is released in the presence of 0.1N HCl within about 15 minutes may be released in the presence 0.1N HCl and 40% ethanol within about 15 minutes. In other embodiments, less than about 60% of the oxycodone that is released in the presence of 0.1N HCl within about 30 minutes may be released in the presence of 0.1N HCl and 40% ethanol within about 30 minutes. In additional embodiments, less than about 75% of the oxycodone that is released in the presence of 0.1N HCl within about 2 hours may be released in the presence 0.1N HCl and 40% ethanol within about 2 hours.

Further, the in vitro release rates of hydrocodone and acetaminophen from the composition generally are not affected by low concentrations of ethanol (e.g., 5% v/v or 20% v/v) when measured in 900 mL of 0.1 N HCl containing the desired percentage of ethanol using a USP type II paddle apparatus and at a constant temperature of 37° C. and about

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150 rpm. For example, from about 25% to about 35% of hydrocodone and about 50% to about 55% of acetaminophen may be released from the composition within about 15 minutes when measured in the presence of 5% to 20% ethanol, and from about 50% to about 65% of hydrocodone and from about 60% to about 70% of acetaminophen may be released from the composition within about 2 hours when measured in the presence of 5% to 20% ethanol.

The in vitro release rates of hydrocodone and acetaminophen from the composition generally are reduced, however, in the presence of 40% ethanol. For example, from about 5% to about 15% of the hydrocodone and from about 15% to about 30% of the acetaminophen may be released from the composition within about 15 minutes when measured in the presence of 40% ethanol, and from about 30% to about 45% of hydrocodone and from about 45% to about 55% of acetaminophen may be released from the composition within about 2 hours when measured in the presence of 40% ethanol.

Stated another way, less hydrocodone is extracted from the composition by a solution of 0.1N HCl and 40% ethanol than is extracted by a solution of 0.1N HCl. In some embodiments, less than about 75% of the hydrocodone that is released in the presence of 0.1N HCl is released in the presence 0.1N HCl containing 40% ethanol. In additional embodiments, less than about 70%, 65%, 60%, 55%, 50%, 45%, or 40% of the hydrocodone that may be released in the presence of 0.1N HCl is released in the presence 0.1N HCl and 40% ethanol. For example, less than about 40% of the hydrocodone that is released in the presence of 0.1N HCl within about 15 minutes may be released in the presence 0.1N HCl and 40% ethanol within about 15 minutes. In other embodiments, less than about 60% of the hydrocodone that is released in the presence of 0.1N HCl within about 30 minutes may be released in the presence of 0.1N HCl and 40% ethanol within about 30 minutes. In additional embodiments, less than about 75% of the hydrocodone that is released in the presence of 0.1N HCl within about 2 hours may be released in the presence 0.1N HCl and 40% ethanol within about 2 hours.

(ii) Stability Data for the Pharmaceutical Composition

In one embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in any amount up to and including, but no more than, about 100 ppm. In other embodiments, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In still another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.6 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In still another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm, 0.3 ppm, 0.4 ppm, 0.5 ppm, 0.6 ppm, 0.7 ppm, 0.8 ppm, 0.9 ppm, 1.0 ppm, 1.1 ppm, 1.2 ppm, 1.3 ppm, 1.4 ppm, 1.5 ppm, 1.6 ppm, 1.7 ppm, 1.8 ppm, 1.9 ppm, 2.0 ppm, 2.1 ppm, 2.2 ppm, 2.3 ppm, 2.4 ppm, 2.5 ppm, 2.6 ppm, 2.7 ppm, 2.8 ppm, 2.9 ppm, 3.0 ppm, 3.1 ppm, 3.2 ppm, 3.3 ppm, 3.4 ppm, 3.5 ppm, 3.6 ppm, 3.7 ppm, 3.8 ppm, 3.9 ppm, 4.0 ppm, 4.1 ppm, 4.2 ppm, 4.3 ppm, 4.4 ppm, 4.5 ppm, 4.6 ppm, 4.7 ppm, 4.8 ppm, 4.9 ppm, 5.0 ppm, 5.1 ppm, 5.2 ppm, 5.3 ppm, 5.4 ppm, 5.5 ppm, 5.6 ppm, 5.7 ppm, 5.8 ppm, 5.9 ppm, and 6.0

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ppm after storage for about 1, 2, or 3 months at a temperature of 25° C. to about 40° C. and at about 60% to about 75% relative humidity

In one embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in any amount up to and including about 0.5% by weight of the oxycodone. In other embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to 40° C. and at about 60% to 75% relative humidity. In still another embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to 40° C. and at about 60% to 75% relative humidity. In additional embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, Related Substance A (i.e., C-Normorphinan-6-carboxylic acid, 4,5-epoxy-6,14-dihydroxy-3-methoxy-17-methyl-, (5 α ,6 α)-) may be present in the pharmaceutical composition as a degradation product of oxycodone in a maximum amount of about 0.5% by weight of the oxycodone. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition in any amount up to about 0.15% by weight of the acetaminophen. In another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In other embodiments, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%,

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0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, and 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in a maximum amount of about 0.2% by weight of the oxycodone. In other embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01% to about 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In further embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, and 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, the total acetaminophen degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the acetaminophen. In other embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In further embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, the total oxycodone degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the oxycodone. In further embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet other embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05% 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

(iii) In Vivo and Pharmacokinetic Properties of the Exemplary Compositions

The composition comprises at least one immediate release portion for immediate release of either oxycodone or hydrocodone and acetaminophen such that therapeutic plasma concentrations are quickly attained (i.e., within one hour) upon oral administration to a subject. The composition also comprises at least one extended release portion for sustained release of either oxycodone or hydrocodone and acetaminophen over an extended period of time, e.g., about 3 to about 12 hours, or about 4 to about 9 hours, or at least about 6 hours,

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or at least about 8 hours, to the upper gastrointestinal tract where acetaminophen, and potentially oxycodone and hydrocodone, are best absorbed.

The composition may be orally administered to a subject once in a 24 hour period (q.d. or once-daily), two times in a 24 hour period (b.i.d. or twice-daily), or three times in a 24 hour period (t.i.d. or three times daily). In one embodiment, the composition may be orally administered to the subject twice a day (i.e., every 12 hours). The subject may be a mammal, and preferably the subject is a human.

In another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition. This first or loading dose may assist the subject in more quickly attaining steady state blood levels of the active drugs. In a further embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising about 22.5 mg of opioid and about 975 mg of an additional active ingredient. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 tablets, each tablet comprising about 11.25 mg of opioid and about 462.5 mg of an additional active ingredient. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 tablets, each tablet comprising about 7.5 mg of opioid and about 325 mg of an additional active ingredient. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 tablets, each tablet comprising about 5.625 mg of opioid and about 231.25 mg of an additional active ingredient. In one embodiment, the opioid contained in the tablet is either oxycodone or hydrocodone, and the additional active ingredient is acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 capsules, each capsule comprising about 11.25 mg of opioid and about 462.5 mg of an additional active ingredient. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 capsules, each capsules comprising about 7.5 mg of opioid and about 325 mg of an additional active ingredient. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 capsules, each capsules comprising about 5.625 mg of opioid and about 231.25 mg of an additional active ingredient. In one embodiment, the opioid contained in the capsule is either oxycodone or hydrocodone, and the additional active ingredient is acetaminophen.

Upon oral administration to a subject, the composition disclosed herein may maintain a therapeutic blood plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hours to about 12 hours after administration of the composition. In another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition. In still another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 1 hour to about 12 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 2 hours to about 10 hours after administration of the composition. In yet another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 1 hour to about 10 hours after administration of the composition. In still another embodiment, the plasma concentration of oxycodone may be maintained at a concentra-

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tion of at least about 10 ng/mL from about 0.75 hour to about 10 hours after administration of the composition.

In another embodiment, the composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} (peak plasma concentration) for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg. In another embodiment, the mean C_{max} for oxycodone may range from about 1.0 ng/mL/mg to about 1.5 ng/mL/mg. In an additional embodiment, the mean C_{max} for oxycodone may be 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, or 1.6 ng/mL/mg. Moreover, the mean C_{max} for oxycodone at steady state may range from about 1.5 ng/mL/mg to about 2.0 ng/mL/mg, from about 1.6 ng/mL/mg to about 1.95 ng/mL/mg, or from about 1.7 ng/mL/mg to about 1.85 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a plasma profile characterized by a biphasic absorption of oxycodone. Deconvolution of the pharmaceutical composition and the target plasma profiles can be done in WinNonLin (version 5.2, Pharsight Corp., Mountain View, Calif.). The results of such a deconvolution analysis for oxycodone is depicted in FIG. 23. The biphasic absorption of oxycodone may be characterized by an initial rapid absorption resulting in a first peak in plasma concentrations between about 1 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours as a result of slower absorption taking place from the at least one extended release portion after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic absorption of oxycodone may be characterized by a plasma concentration-time profile for oxycodone in which the slope of a line drawn between 0 hour and 2 hour is greater than the slope of a line drawn between about 2 hours and 5 hours. See FIG. 23.

This biphasic increase in oxycodone levels resulting from the composition has several benefits. For example, providing rapid but not too high concentrations of oxycodone for quick onset of analgesia followed by maintenance of oxycodone levels over an extended time period could prevent a human subject from developing liking or dependence (abuse) for oxycodone. Further fluctuations in the oxycodone plasma levels could also prevent development of tolerance at the active site. Thus, the biphasic increase in oxycodone levels helps to prevent this acute tolerance.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for oxycodone from about 9.0 ng·hr/mL/mg to about 18.5 ng·hr/mL/mg. In a further embodiment, the mean AUC for oxycodone may be from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg. In another embodiment, the mean AUC for oxycodone may be about 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, or 16.0 ng·hr/mL/mg. Additionally, the mean AUC for oxycodone at steady state may range from about 11.0 ng·hr/mL/mg to about 17.0 ng·hr/mL/mg, from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} (time to peak plasma concentration) for oxycodone from about 2.0 hours to about 7.0 hours. In an alternate embodiment, the median T_{max} for oxycodone may be from about 3.0 hours to about 6.0 hours. In another embodiment, the median T_{max} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 or 6.0 hours.

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Moreover, the median T_{max} for oxycodone at steady state may range from about 1.5 hours to about 3.5 hours, or from about 2 hours to about 3 hours.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median t_{lag} for oxycodone from about 0 hours to about 0.5 hours. In an alternate embodiment, the median t_{lag} for oxycodone may be from about 0 hours to about 0.25 hours.

Rates of absorption are often assessed by comparing standard pharmacokinetic parameters such as T_{max} and C_{max}. The extent of absorption is assessed by the AUC. A short T_{max} has been used to indicate rapid absorption. The U.S. FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (March 2003) and related publications (Chen et al, Clin. Pharmacokinet. 40(8):565-72, 2001) also recommends the use of partial AUC for some modified-release drugs ("MR drugs"), such as the pharmaceutical compositions disclosed herein. A partial AUC calculation may be used to measure early exposure to a drug, which may signify an initial onset of pain relief and/or to measure prolonged exposure of a drug in achieving sustained relief. Partial AUC calculations can also demonstrate whether two MR drugs are truly bioequivalent by comparing, for example, an early partial AUC, which will be associated with a drug's response onset, and a late partial AUC, which will be associated with a drug's sustained response. The parameters for compositions vary greatly between subjects. The parameters also vary depending on aspects of the study protocol such as the sampling scheduling, subject posture and general subject health. Values quoted in this specification are given as mean±standard deviation unless otherwise noted.

For partial AUC calculations, the standard linear trapezoidal summation over each time interval is used. The partial AUCs are calculated from the mean pharmacokinetic profile. For time 0 to 1 hour the partial AUC is AUC_(0-1hr); for time 0 to 2 hours the partial AUC is AUC_(0-2hr); for time 0-4 hours the partial AUC is AUC_(0-4hr); for time 0 to 6 hour the partial AUC is AUC_(0-6hr); for time 0 to 8 hours the partial AUC is AUC_(0-8hr); and for time 0 to the last measurable time point ("x") the partial AUC is AUC_{(0-(x)hr)} where each partial AUC is calculated according to standard pharmaceutical industry pharmacokinetic calculation methodologies as given by:

AUC_(0-1hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 1 hour.

AUC_(0-2hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 2 hours.

AUC_(0-4hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 4 hours.

AUC_(0-6hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 6 hour.

AUC_(0-8hr)—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 8 hours.

AUC_{(0-(t)hr)}—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the last measurable time point.

AUC_{(0-(T_{max} of IR product+2SD))}—Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations ("2SD") for the immediate release drug.

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The FDA has identified this calculation in association with an early onset of response for modified-release dosage forms. (See *supra* March 2003 Guidance; Draft Guidance on Dexamethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (November 2011)).

$AUC_{((T_{max} \text{ of IR product} + 2SD) - t)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations (“2SD”) for the immediate release drug to the last measurable time point. The FDA has identified this parameter in association with sustaining the response for modified-release dosage forms. (See March 2003 Guidance *supra*; Draft Guidance on Dexamethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (November 2011)).

$AUC_{(x-(y)hr)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time “x” (e.g., any measurable time point, such as 8 hours) to time “y” (e.g., any other measurable time point later than “x”, such as 12 hours).

$AUC_{(0-\infty)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time 0 to infinity.

Further, partial AUC may be calculated using trapezoidal summation from time T_{max} to time t (the last measured time point of plasma concentration profile).

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for oxycodone from about 0.10 ng·hr/mL/mg to about 0.45 ng·hr/mL/mg, from about 0.15 ng·hr/mL/mg to about 0.25 ng·hr/mL/mg, or from about 0.25 ng·hr/mL/mg to about 0.35 ng·hr/mL/mg. In another embodiment, the AUC_{0-1hr} for oxycodone may be about 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, or 0.45 ng·hr/mL/mg.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.65 ng·hr/mL/mg to about 1.35 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be about 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30 or 1.35 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for oxycodone from about 2.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, from about 2.5 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, or 4.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{T_{max}-t}$ for oxycodone from about 5.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, from about 8.0 ng·hr/mL/mg to about 10.5 ng·hr/mL/mg, or from about 10.5 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg. In another embodiment, the $AUC_{T_{max}-t}$ for oxycodone may be about 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0 or 16.0 ng·hr/mL/mg.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-(T_{max} \text{ of IR product} + 2SD))}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg,

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from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(T_{max} \text{ of IR product} + 2SD))}$ for oxycodone may be about 1.0, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product} + 2SD))}$:

$$\text{oxycodone mean} \pm \text{SD} = 1.0 \text{ h} \pm 0.89 \text{ h}; T_{max} + 2SD = 2.8 \text{ hours}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-2.8)}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-2.8)}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(2.8-4.8)}$ for oxycodone after a single dose from about 7.5 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, from about 8.45 ng·hr/mL/mg to about 13.7 ng·hr/mL/mg, or from about 9.5 ng·hr/mL/mg to about 11.5 ng·hr/mL/mg. In another embodiment, the $AUC_{(2.8-4.8)}$ for oxycodone may be about 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, or 12.5 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product} + 2SD))}$:

$$\text{oxycodone mean} \pm \text{SD} = 1.9 \text{ h} \pm 1.2 \text{ h}; T_{max} + 2SD = 4.3 \text{ hours}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $MX_{(0-4.3)}$ for oxycodone after a single dose from about 1.5 ng·hr/mL/mg to about 5.5 ng·hr/mL/mg, from about 2.0 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, from about 2.5 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-4.3)}$ for oxycodone may be about 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, 3.5, 3.55, 3.6, 3.65, 3.7, 3.75, 3.8, 3.85, 3.9, 3.95, 4.0, 4.05, 4.1, 4.15, 4.2, 4.25, 4.3, 4.35, 4.4, 4.45, 4.5, 4.55, 4.6, 4.65, 4.7, 4.75, 4.8, 4.85, 4.9, 4.95, 5.0, 5.05, 5.1, 5.15, 5.2, 5.25, 5.3, 5.35, 5.4, 5.45, or 5.5 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(4.3-4.8)}$ for oxycodone after a single dose from about 5.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 13.5 ng·hr/mL/mg, from about 9.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 9.5 ng·hr/mL/mg to about 11.5 ng·hr/mL/mg. In another embodiment, the $AUC_{(4.3-4.8)}$ for oxycodone may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1,

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7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject in a fasted state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 3% to about 33% of the AUC_{0-r} , from about 10% to about 27% of the AUC_{0-r} , or from about 15% to about 22% of the AUC_{0-r} . In another embodiment, the pharmaceutical composition, when orally administered to a subject in a fed state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 5% to about 35% of the AUC_{0-r} , from about 12% to about 30% of the AUC_{0-r} , or from about 15% to about 25% of the AUC_{0-r} .

In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may provide a mean half-life of oxycodone that ranges from about 3.5 hours to about 5.5 hours, or more preferably from about 4 hours to about 5 hours. In various embodiments, the mean half-life of oxycodone may be about 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, or 5.2 hours.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an abuse quotient for oxycodone from about 3 to about 5. In other embodiments, the abuse quotient for oxycodone may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0.

Further, upon oral administration to a subject, the composition disclosed herein may maintain a therapeutic blood plasma concentration of hydrocodone of at least about 5 ng/mL from about 0.75 hours to about 20 hours after administration of the composition. In another embodiment, the plasma concentration of hydrocodone may be maintained at a concentration of at least about 7.5 ng/mL from about 1 hour to about 12 hours after administration of the composition. In a further embodiment, the plasma concentration of hydrocodone may be maintained at a concentration of at least about 10 ng/mL from about 2 hour to about 10 hours after administration of the composition. In yet another embodiment, the plasma concentration of hydrocodone may be maintained at a concentration of at least about 10 ng/mL from about 0.75 hour to about 10 hours after administration of the composition.

In another embodiment, the composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} (peak plasma concentration) for hydrocodone from about 0.9 ng/mL/mg to about 2.0 ng/mL/mg. In another embodiment, the mean C_{max} for hydrocodone may range from about 1.0 ng/mL/mg to about 1.6 ng/mL/mg. In an additional embodiment, the mean C_{max} for hydrocodone may be 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0 ng/mL/mg. Moreover, the mean C_{max} for hydrocodone at steady state may range from about 1.3 ng/mL/mg to about 2.0 ng/mL/mg, from about 1.5 ng/mL/mg to about 1.95 ng/mL/mg, or from about 1.6 ng/mL/mg to about 1.85 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a plasma profile characterized by a biphasic absorption

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of hydrocodone. Deconvolution of the pharmaceutical composition and the target plasma profiles can be done in WinNonLin (version 5.2, Pharsight Corp., Mountain View, Calif.). The biphasic absorption of hydrocodone may be characterized by an initial rapid absorption resulting in a first peak in plasma concentrations between about 1 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours as a result of slower absorption taking place from the at least one extended release portion after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic absorption of hydrocodone may be characterized by a plasma concentration-time profile for hydrocodone in which the slope of a line drawn between 0 hour and 2 hour is greater than the slope of a line drawn between about 2 hours and 5 hours.

This biphasic increase in hydrocodone levels resulting from the composition has several benefits. For example, providing rapid but not too high concentrations of hydrocodone for quick onset of analgesia followed by maintenance of hydrocodone levels over an extended time period could prevent a human subject from developing liking or dependence (abuse) for hydrocodone. Further fluctuations in the hydrocodone plasma levels could also prevent development of tolerance at the active site. Thus, the biphasic increase in hydrocodone levels helps to prevent this acute tolerance.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for hydrocodone from about 9.0 ng·hr/mL/mg to about 24.0 ng·hr/mL/mg. In a further embodiment, the mean AUC for hydrocodone may be from about 10.0 ng·hr/mL/mg to about 22.0 ng·hr/mL/mg. In another embodiment, the mean AUC for hydrocodone may be about 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, 17.0, 17.5, 18.0, 18.5, 19.0, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, or 24.0 ng·hr/mL/mg. Additionally, the mean AUC for hydrocodone at steady state may range from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, from about 12.0 ng·hr/mL/mg to about 19.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 18.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} (time to peak plasma concentration) for hydrocodone from about 2.0 hours to about 8.0 hours. In an alternate embodiment, the median T_{max} for hydrocodone may be from about 3.0 hours to about 6.0 hours. In another embodiment, the median T_{max} for hydrocodone may be about 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, or 8.0 hours. Moreover, the median T_{max} for hydrocodone at steady state may range from about 1.5 hours to about 5.0 hours, or from about 2 hours to about 4 hours.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median t_{lag} for hydrocodone from about 0 hours to about 0.5 hours. In an alternate embodiment, the median t_{lag} for hydrocodone may be from about 0 hours to about 0.33 hours.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0)-(T_{max} \text{ of IR product} + 2SD)}$ for hydrocodone after a single dose from about 1.0 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 4.25 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg. In another embodiment, the

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$AUC_{0-(T_{max}+2SD \text{ of IR product})}$ for hydrocodone may be about 1.0, 1.25, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, or 3.5 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for hydrocodone after a single dose from about 1.0 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 4.25 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-3hr)}$ for hydrocodone may be about 1.0, 1.25, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, or 3.5 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-2.44hr)}$ for hydrocodone after a single dose from about 0.5 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, from about 1.0 ng·hr/mL/mg to about 4.25 ng·hr/mL/mg, or from about 1.5 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-2.44hr)}$ for hydrocodone may be about 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, 1.0, 1.05, 1.1, 1.15, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, or 3.5 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for hydrocodone from about 5 ng·hr/mL/mg to about 25 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 15.5 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 12.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for hydrocodone from about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, or 20.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for hydrocodone from about 3 ng·hr/mL/mg to about 20 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, or from about 8 ng·hr/mL/mg to about 12.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for hydrocodone from about 3.0, 4.0, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6,

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12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, or 20.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for hydrocodone from about 2 ng·hr/mL/mg to about 10 ng·hr/mL/mg, from about 4 ng·hr/mL/mg to about 8 ng·hr/mL/mg, and from about 6 ng·hr/mL/mg to about 7 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for hydrocodone from about 2.0, 2.5, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for hydrocodone from about 1 ng·hr/mL/mg to about 6 ng·hr/mL/mg, from about 2 ng·hr/mL/mg to about 5 ng·hr/mL/mg, or from about 3 ng·hr/mL/mg to about 4 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for hydrocodone from about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, 3.5, 3.55, 3.6, 3.65, 3.7, 3.75, 3.8, 3.85, 3.9, 3.95, 4.0, 4.05, 4.1, 4.15, 4.2, 4.25, 4.3, 4.35, 4.4, 4.45, 4.5, 4.55, 4.6, 4.65, 4.7, 4.75, 4.8, 4.85, 4.9, 4.95, 5.0, 5.05, 5.1, 5.15, 5.2, 5.25, 5.3, 5.35, 5.4, 5.45, 5.5, 5.55, 5.6, 5.65, 5.7, or 5.75 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{T_{max}+2SD-36hr}$ for hydrocodone from about 5 ng·hr/mL/mg to about 25 ng·hr/mL/mg, from about 10 ng·hr/mL/mg to about 20 ng·hr/mL/mg, or from about 13 ng·hr/mL/mg to about 17 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{3-36hr} for hydrocodone from about 5.0, 5.25, 5.50, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.5, 7.75, 8.0, 8.25, 8.5, 8.75, 9.0, 9.25, 9.5, 9.75, 10.0, 10.25, 10.5, 10.75, 11.0, 11.25, 11.5, 11.75, 12.0, 12.25, 12.5, 12.75, 13.0, 13.25, 13.5, 13.75, 14.0, 14.25, 14.5, 14.75, 15.0, 15.25, 15.5, 15.75, 16.0, 16.25, 16.50, 16.75, 17.0, 17.25, 17.5, 17.75, 18.0, 18.25, 18.5, 18.75, 19.0, 19.25, 19.5, 19.75, 20.0, 20.25, 20.5, 20.75, 21.0, 21.25, 21.5, 21.75, 22.0, 22.25, 22.5, 22.75, 23.0, 23.25, 23.5, 23.75, 24.0, 24.25, 24.5, 24.75, or 25.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{2.44-36hr}$ for hydrocodone from about 5 ng·hr/mL/mg to about 25 ng·hr/mL/mg, from about 10 ng·hr/mL/mg to about 20 ng·hr/mL/mg, or from about 13 ng·hr/mL/mg to about 17 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{2.44-36hr}$ for hydrocodone from about 5.0,

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5.25, 5.50, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.5, 7.75, 8.0, 8.25, 8.5, 8.75, 9.0, 9.25, 9.5, 9.75, 10.0, 10.25, 10.5, 10.75, 11.0, 11.25, 11.5, 11.75, 12.0, 12.25, 12.5, 12.75, 13.0, 13.25, 13.5, 13.75, 14.0, 14.25, 14.5, 14.75, 15.0, 15.25, 15.5, 15.75, 16.0, 16.25, 16.50, 16.75, 17.0, 17.25, 17.5, 17.75, 18.0, 18.25, 18.5, 18.75, 19.0, 19.25, 19.5, 19.75, 20.0, 20.25, 20.5, 20.75, 21.0, 21.25, 21.5, 21.75, 22.0, 22.25, 22.5, 22.75, 23.0, 23.25, 23.5, 23.75, 24.0, 24.25, 24.5, 24.75, or 25.0 ng-hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for hydrocodone from about 50% to about 90% of the AUC_{0-r} from about 55% to about 80% of the AUC_{0-r} , or from about 60% to about 70% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for hydrocodone that is about 50%, about 53%, about 55%, about 58%, about 60%, about 63%, about 65%, about 68%, about 70%, about 73%, about 75%, about 78%, about 80%, about 83%, about 85%, about 88%, or about 90% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for hydrocodone from about 40% to about 90% of the AUC_{0-r} from about 55% to about 80% of the AUC_{0-r} , or from about 60% to about 70% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for hydrocodone of about 40%, about 43%, about 45%, about 48%, about 50%, about 53%, about 55%, about 58%, about 60%, about 63%, about 65%, about 68%, about 70%, about 73%, about 75%, about 78%, about 80%, about 83%, about 85%, about 88%, or about 90% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for hydrocodone from about 20% to about 50% of the AUC_{0-r} from about 25% to about 45% of the AUC_{0-r} , or from about 30% to about 40% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for hydrocodone of about 20%, about 23%, about 25%, about 28%, about 30%, about 33%, about 35%, about 38%, about 40%, about 43%, about 45%, about 48%, about 50%, or about 53% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for hydrocodone from about 5% to about 30% of the AUC_{0-r} from about 10% to about 25% of the AUC_{0-r} , or from about 15% to about 20% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for hydrocodone of about 5%, about 8%, about 10%, about 13%, about 15%, about 18%, about 20%, about 23%, about 25%, about 28%, or about 30% of the AUC_{0-r} .

Moreover, upon oral administration, the pharmaceutical composition disclosed herein may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 1 hour to about 6 hours after administration. In another embodiment, the pharmaceutical composition may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 0.75 hour to about 6.5 hours after administration. In yet another embodiment, the composition may maintain a plasma con-

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centration of acetaminophen of at least about 1 mg/mL from about 0.5 hour to about 12 hours after administration.

In another embodiment, the composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg. In other embodiments, the mean C_{max} for acetaminophen may be from about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, or 11.0 ng/mL/mg. Moreover, the mean C_{max} for acetaminophen at steady state may range from about 6.0 ng/mL/mg to about 9.0 ng/mL/mg, from about 6.5 ng/mL/mg to about 8.5 ng/mL/mg, or from about 7.0 ng/mL/mg to about 8.0 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a plasma profile characterized by a biphasic absorption of acetaminophen. The biphasic absorption of acetaminophen may be characterized by an initial rapid absorption resulting in first peak in plasma concentrations between about 0.5 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic absorption of acetaminophen may be characterized by a plasma concentration-time profile for acetaminophen in which the slope of a line drawn between 0 hour and 2 hour is greater than the slope of a line drawn between about 2 hours and 5 hours. See FIG. 24.

This biphasic increase in acetaminophen levels resulting from the composition has several benefits. For example, the initial rapid rise in plasma levels produce quick onset of analgesia and the slower absorption provides maintenance of analgesia for an extended period of time.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for acetaminophen from about 35.0 ng-hr/mL/mg to about 80.0 ng-hr/mL/mg. In a further embodiment, the mean AUC for acetaminophen from about 35.0 ng-hr/mL/mg to about 60.0 ng-hr/mL/mg. In other embodiments, the mean AUC for acetaminophen may be about 35.0, 40.0, 45.0, 50.0, 55.0, 60.0, 65.0, 70.0, 75.0, or 80.0 ng-hr/mL/mg. Additionally, the mean AUC for acetaminophen at steady state may range from about 40.0 ng-hr/mL/mg to about 50.0 ng-hr/mL/mg, from about 35.0 ng-hr/mL/mg to about 45.0 ng-hr/mL/mg, or from about 37.0 ng-hr/mL/mg to about 42.0 ng-hr/mL/mg.

In yet another embodiment, the pharmaceutical composition when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} for acetaminophen from about 0.5 hours to about 6.0 hours. In another embodiment, the median T_{max} for acetaminophen may range from about 1.0 hour to about 5.0 hours. In a further embodiment, the median T_{max} for acetaminophen may range from about 0.5 hour to about 4.0 hours. In still another embodiment, the median T_{max} for acetaminophen may range from about 0.75 to about 1.5 hours. In other embodiments, the median T_{max} may be about 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 hours. Moreover, the median T_{max} for acetaminophen at steady state may range from about 0.5 hours to about 1.0 hour, or from about 0.5 hours to about 0.75 hours.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median t_{lag} for acetaminophen

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from about 0 hours to about 0.5 hours. In an alternate embodiment, the median tlag for acetaminophen may be from about 0 hours to about 0.25 hours. In one embodiment, the median tlag for acetaminophen may be 0 hour. In another embodiment, the median tlag for acetaminophen may be 0.25 hour.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a plasma profile characterized by various partial AUCs for acetaminophen. The partial AUCs for acetaminophen are calculated as described above for oxycodone. The pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for acetaminophen from about 1.25 ng·hr/mL/mg to about 3.25 ng·hr/mL/mg, from about 1.60 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 2.75 ng·hr/mL/mg. In another embodiment, the AUC_{0-1hr} for acetaminophen may be about 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, 2.30, 2.35, 2.40, 2.45, 2.50, 2.55, 2.60, 2.65, 2.70, 2.75, 2.80, 2.85, or 2.90 ng·hr/mL/mg.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 4.25 ng·hr/mL/mg to about 8.75 ng·hr/mL/mg, from about 5.50 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 6.0 ng·hr/mL/mg to about 7.25 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen may be about 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.50, 7.75 or 8.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for acetaminophen from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, from about 13.0 ng·hr/mL/mg to about 14.5 ng·hr/mL/mg, or from about 14.5 ng·hr/mL/mg to about 16.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for acetaminophen may be about 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, or 17.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{Tmax-t} for acetaminophen from about 20.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg, from about 23.5 ng·hr/mL/mg to about 36.0 ng·hr/mL/mg, or from about 29.0 ng·hr/mL/mg to about 31.0 ng·hr/mL/mg. In another embodiment, the AUC_{Tmax-t} for acetaminophen may be about 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5 or 36.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$ for acetaminophen may be about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$:

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acetaminophen mean±SD=0.596 h±0.529 h; $T_{max} + 2SD = 1.65$ hour

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-1.7)}$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-1.7)}$ for acetaminophen may be about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(1.7-48)}$ for acetaminophen after a single dose from about 25.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 31.5 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(1.7-48)}$ for acetaminophen may be about 25, 26, 27, 28, 29, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(Tmax \text{ of IR product} + 2SD))}$:

acetaminophen mean±SD=1.48 h±0.875 h; $T_{max} + 2SD = 3.2$ hour

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3.2)}$ for acetaminophen after a single dose from about 7.0 ng·hr/mL/mg to about 21.0 ng·hr/mL/mg, from about 9.0 ng·hr/mL/mg to about 18.0 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-3.2)}$ for acetaminophen may be about 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, or 21.0 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3.2-48)}$ for acetaminophen after a single dose from about 15.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, from about 27.5 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 30.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(3.2-48)}$ for acetaminophen may be about 15.0, 15.5, 16.0, 16.5, 17.0, 17.5, 18.0, 18.5, 19.0, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0,

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27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, 55.0, 55.5, 56.0, 56.5, 57.0, 57.5, 58.0, 58.5, 59.0, 59.5, 60.0, 60.5, 61.0, 61.5, 62.0, 62.5, 63.0, 63.5, 64.0, 64.5, 65.0, 65.5, 66.0, 66.5, 67.0, 67.5, 68.0, 68.5, 69.0, 69.5, 70.0, 70.5, 71.0, 71.5, 72.0, 72.5, 73.0, 73.5, 74.0, 74.5, or 75.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-1.27)}$ for acetaminophen after a single dose from about 3.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 4.0 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 5.0 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-1.27)}$ for acetaminophen may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, or 13 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(1.27-3.6)}$ for acetaminophen after a single dose from about 20.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 65.0 ng·hr/mL/mg, or from about 30.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(1.27-3.6)}$ for acetaminophen may be about 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, 55.0, 55.5, 56.0, 56.5, 57.0, 57.5, 58.0, 58.5, 59.0, 59.5, 60.0, 60.5, 61.0, 61.5, 62.0, 62.5, 63.0, 63.5, 64.0, 64.5, 65.0, 65.5, 66.0, 66.5, 67.0, 67.5, 68.0, 68.5, 69.0, 69.5, 70.0, 70.5, 71.0, 71.5, 72.0, 72.5, 73.0, 73.5, 74.0, 74.5, or 75.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0 ng·hr/mL/mg to about 60.0 ng·hr/mL/mg, from about 30 ng·hr/mL/mg to about 50 ng·hr/mL/mg, from about 35 to about 45 ng·hr/mL/mg, or from about 37.5 ng·hr/mL/mg to about 42.5 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0. In a further embodiment, at AUC_{0-12hr} between about 70%-95%, about 75%-92%, or about 77%-90% of the acetaminophen has been cleared. In still another embodiment, about 80% of the acetaminophen has been cleared.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen

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from about 15.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 30.0 to about 40.0 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, or 50.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 5.0 ng·hr/mL/mg to about 25.0 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, or from about 10.0 ng·hr/mL/mg to about 15.0. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, or 17.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5 ng·hr/mL/mg to about 15.5 ng·hr/mL/mg, from about 2 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg, from about 3.5 ng·hr/mL/mg to about 10 ng·hr/mL/mg, or from about 4.5 ng·hr/mL/mg to about 6.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for acetaminophen from about 1.5 ng·hr/mL/mg to about 15.5 ng·hr/mL/mg, from about 2 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg, from about 3.5 ng·hr/mL/mg to about 10 ng·hr/mL/mg, or from about 4.5 to about 6.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for acetaminophen from about 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5,

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9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{0-1.27hr}$ for acetaminophen from about 15.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, or from about 30.0 to about 45.0 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{0-1.27hr}$ for acetaminophen from about 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, or 50.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{1.27-3.6hr}$ for acetaminophen from about 1.5 ng·hr/mL/mg to about 15.5 ng·hr/mL/mg, from about 2 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg, from about 3.5 ng·hr/mL/mg to about 10 ng·hr/mL/mg, or from about 4.5 to about 7.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{1.27-3.6hr}$ for acetaminophen from about 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for acetaminophen from about 5 ng·hr/mL/mg to about 30 ng·hr/mL/mg, from about 10 ng·hr/mL/mg to about 20 ng·hr/mL/mg, or from about 13 ng·hr/mL/mg to about 17 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for acetaminophen from about 5.0, 6.0, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, or 20.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3-3.6hr)}$ for acetaminophen from about 20 ng·hr/mL/mg to about 50 ng·hr/mL/mg, from about 20 ng·hr/mL/mg to about 40 ng·hr/mL/mg, or from about 25 ng·hr/mL/mg to about 35 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3-3.6hr)}$ for acetaminophen from about 20,

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20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5, or 50 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 50% to about 90% of the AUC_{0-r} , from about 55% to about 85% of the AUC_{0-r} , or from about 75% to about 85% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen that is about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84% or 85% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 40% to about 90% of the AUC_{0-r} , from about 55% to about 85% of the AUC_{0-r} , or from about 60% to about 75% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen of about 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 10% to about 40% of the AUC_{0-r} , from about 15% to about 35% of the AUC_{0-r} , or from about 20% to about 30% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen of about 10%, 12%, 14%, 16%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 5% to about 30% of the AUC_{0-r} , from about 7% to about 25% of the AUC_{0-r} , or from about 10% to about 20% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen of about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of the AUC_{0-r} .

In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 2 hours to about 10 hours, or more preferably from about 3 hours to about 6 hours. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 3 hours to about 5 hours. In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 4 hours to about 5 hours. In various embodiments, the mean half-life of acetaminophen may be about 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, or 8 hours. In additional embodiments, the pharmaceutical composition, when orally administered to a subject, has a mean

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observed half-life of acetaminophen that is more than the mean half-life of commercially available immediate release acetaminophen products.

In another embodiment, upon administration of the pharmaceutical composition to a subject, the composition may provide at least about 4 hours to about 12 hours of drug delivery to the upper gastrointestinal tract, which includes the duodenum, jejunum, and ileum of the small intestine. In another embodiment, the composition may provide at least about 6 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 8 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 9 hours, or at least about 10 hours of drug delivery to the upper gastrointestinal tract.

In yet another embodiment, upon administration of the pharmaceutical composition to a subject, the additional API undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to pre-systemic metabolism is referred to as the fraction absorbed and denoted "Fab." This is different from the fraction bioavailable "F," which is the fraction that reaches the systemic circulation after the metabolism in the gut and liver.

In another embodiment, 60-90% of the acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 60-85% of acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See FIG. 27. Greater than 50% absorption of acetaminophen in the upper gastrointestinal tract is beneficial to a human subject because acetaminophen is poorly absorbed in the stomach and well absorbed in the small intestine and particularly, the upper segment of the gastrointestinal tract. It is therefore critical that acetaminophen is available in upper small intestine for its absorption. In one embodiment acetaminophen is released in stomach and reaches quickly into upper GIT for the absorption to take place.

In another embodiment, when about 60% to about 75% of the acetaminophen is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 27), about 15% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 27), and about 5% to about 15% is absorbed in the ileum.

In another embodiment, when about 70% to about 90% of the acetaminophen is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 27), about 15% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 27), and about 5% to about 15% is absorbed in the ileum.

In yet another embodiment, when at least about 55% of the total amount of the acetaminophen is released from the dosage form in the stomach within 1 hour after oral administration and when at least about 60% of the acetaminophen is released in the stomach after 2 hours, about 15% to about 20% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circula-

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tion, is absorbed in the duodenum, about 30% to about 37% is absorbed in the proximal jejunum, about 15% to about 18% is absorbed in the distal jejunum, and about 8% to about 10% is absorbed in the ileum.

In still another embodiment, upon administration of the pharmaceutical composition to a subject, the opioid undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug absorbed into the systemic circulation. This is referred to as the fraction absorbed and denoted "Fab." In one embodiment, the opioid is oxycodone. In another embodiment, the opioid is hydrocodone.

In a further embodiment, 70-95% of the oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 80-95% of oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See FIG. 28.

In one embodiment, the composition releases the opioid and other API in the stomach to optimize drug absorption in the duodenum and jejunum. For example, when about 25% to about 50% of oxycodone is released from the dosage form in the stomach within 1 hour following oral administration, about 10% to about 45% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 50% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 7% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 15% is absorbed in the ileum.

In another embodiment, when about 45% to about 65% of oxycodone is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 50% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 55% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 5% to about 25% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 15% is absorbed in the ileum.

In another embodiment, when about 60% to about 85% of oxycodone is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 55% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 30% to about 60% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 10% to about 30% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 20% is absorbed in the ileum.

In yet another embodiment, when at least 25% of the total amount of the oxycodone is released from the dosage form in the stomach within 1 hour after oral administration and when at least 45% of the oxycodone is released in the stomach after 2 hours, about 30% to about 45% of the total amount of oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 37% to about 43% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 10% to about 15% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 8% is absorbed in the ileum.

Under U.S. FDA guidelines, two pharmaceutical products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and Cmax are between 0.80 to 1.25. U.S. FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General*

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Considerations (March 2003). In one embodiment, a common characteristic of the inventive pharmaceutical compositions include bioequivalence established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC.

In one embodiment, the pharmaceutical formulations disclosed herein rapidly achieve therapeutic plasma drug levels of oxycodone and acetaminophen similar to an immediate release product, which provides an early onset of action within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the formulation, but unlike an immediate release product, the pharmaceutical composition is able to maintain those therapeutic plasma drug levels of oxycodone and acetaminophen over an extended period of time (e.g., up to 12 hours). Currently, there is no pharmaceutical composition available comprising oxycodone and acetaminophen, which is able to provide a patient with quick onset of analgesia and maintenance of analgesia for an extended period of time.

In still another embodiment, the pharmaceutical composition rapidly achieves therapeutic plasma drug levels of hydrocodone and acetaminophen similar to an immediate release product, but unlike an immediate release product, the pharmaceutical composition is able to maintain those therapeutic plasma drug levels of hydrocodone and acetaminophen over an extended period of time (e.g., 12 hours). Currently, there is no pharmaceutical composition available comprising hydrocodone and acetaminophen, which is able to provide a patient with quick onset of analgesia and maintenance of analgesia for an extended period of time.

In a further embodiment, the pharmaceutical composition rapidly achieves therapeutic plasma drug levels of opioid and an additional API similar to an immediate release product, but unlike an immediate release product, the pharmaceutical composition is able to maintain those therapeutic plasma drug levels of opioid and the additional API over an extended period of time (e.g., 12 hours).

In yet another embodiment, upon average, within one hour of administration to a subject, the pharmaceutical composition achieves a C_{max} for acetaminophen. The C_{max} achieved by the pharmaceutical composition disclosed herein is comparable to the C_{max} obtained from a commercially-available immediate release product containing acetaminophen formulated at half the strength of the commercially-available immediate release product. The acetaminophen continues to be released from the pharmaceutical composition at a rate less than the clearance rate for the acetaminophen, so that the acetaminophen levels fall smoothly until all of the acetaminophen is absorbed. Stated another way, the acetaminophen released by the pharmaceutical composition is eliminated by the body faster than it is being absorbed. The absorption of the acetaminophen released from the pharmaceutical composition is complete in about 8 to about 10 hours so that for one half life of acetaminophen the blood supply reaching the subject's liver via the portal vein contains no additional amounts of acetaminophen beyond the amounts present in the subject's general circulation.

These additional amounts of acetaminophen delivered to the liver from the subject's portal vein are frequently caused by the absorption of acetaminophen in the subject's gastrointestinal tract. Indeed, blood from the subject's intestines passes through the liver and then on to the general circulation. When acetaminophen is undergoing absorption, blood containing acetaminophen from the absorption process passes through the subject's liver prior to entering the general circulation where the acetaminophen is diluted by the distribution

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and clearance processes. The metabolism of these higher acetaminophen concentrations in blood coming into the subject's liver is termed the "first pass effect." Hence, the absorption process for acetaminophen taxes a subject's metabolic systems in the liver due to these higher "first pass" concentrations. Once the absorption process is complete, the concentration of acetaminophen in the blood reaching the subject's liver through the portal vein will be the same concentration of acetaminophen as found in blood throughout the rest of the subject's body. Thus, the pharmaceutical compositions disclosed herein provide a C_{max} comparable to a commercially-available immediate-release acetaminophen product (dosed at half strength) while providing a less taxing burden on the subject's metabolic systems in the liver because the acetaminophen released by the pharmaceutical composition is eliminated by the subject's body faster than it is being absorbed. This results in decreased levels of acetaminophen in a subject's liver as compared to an immediate release dosage form of acetaminophen dosed every 6 hours.

(iv) The Pharmacokinetic Profiles of the Pharmaceutical Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject

Food can play a significant role in both the rate and extent of absorption of a drug. As is known, the primary function of the small intestine is to absorb food. During and after a meal, the intestine normally shows very irregular or unsynchronized contractions that move the food content back and forth and mix it with the digestive enzymes that are secreted into the intestine. However, these contractions are not entirely unsynchronized; they move the contents of the intestine slowly towards the large intestine. It normally takes about 90-120 minutes for the first part of a meal to reach the large intestine, and the last portion of the meal may not reach the large intestine for five (5) hours. Between meals, the intestine shows cycles of activity that repeat about every 90-120 minutes. The cycle consists of a short period of very few contractions (Phase I), followed by a long period of unsynchronized contractions that appear similar to the fed pattern (pre-burst, Phase II), and then a burst of strong, regular contractions that move down the intestine in a peristaltic fashion (Phase III). Phase III represents a continuation of the "housekeeper waves" that start in the stomach; its function is to sweep undigested food particles and bacteria out of the small intestine and ultimately into the large intestine.

Because non-opioid GR dosage forms of the prior art, as well as prior art extended release opioid formulations, demonstrate food effects, Applicants expected to likewise see a food effect with the pharmaceutical compositions of the present invention. Here, however, Applicants have surprisingly discovered that the pharmacokinetic profiles of the oxycodone and acetaminophen, and the hydrocodone and acetaminophen, are not substantially affected by the fed or fasted state of a human subject ingesting the composition. This means that there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the oxycodone/acetaminophen compositions are administered in the fed versus the fasted state. Without being bound to theory, Applicants believe that in a fasted state the opioid acts to reduce gastric motility in an amount sufficient to retain the dosage form in the stomach thereby mitigating the "housekeeper waves" described above.

As shown in Examples 6 and 9, the pharmacokinetic parameters of the compositions of the invention are similar when the composition is administered in the fed and fasted states. Benefits of a dosage form, which substantially eliminates the effect of food, include an increase in convenience, thereby increasing patient compliance, as the patient does not

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need to ensure that they are taking a dose either with or without food. This is significant because poor patient compliance can lead to adverse therapeutic outcomes.

The invention also encompasses an oxycodone/APAP pharmaceutical composition in which administration of the composition to a human subject in a fasted state is bioequivalent to administration of the composition to a human subject in a fed state wherein bioequivalence is established by: (1) a 90% Confidence Interval (CI) for AUC which is between 80% and 125%, and (2) a 90% CI for C_{max} which is 80% and 125%. In other embodiments, the difference in absorption of the APIs of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

III. Methods for Preparing Solid Dosage Forms

Another aspect of the disclosure provides methods for preparing solid dosage forms of the extended release pharmaceutical composition that provides extended release of oxycodone and acetaminophen. Solid dosage pharmaceutical compositions in the form of tablets may be produced using any suitable method known in the art including but not limited to wet granulation, dry granulation, direct compression, and combinations thereof.

Granulation is a manufacturing process which increases the size and homogeneity of active pharmaceutical ingredients and excipients that comprise a solid dose formulation. The granulation process, which is often referred to as agglomeration, changes important physical characteristics of the dry formulation, with the aim of improving manufacturability and, thereby, product quality, as well as providing desired release kinetics. Wet granulation is by far the more prevalent agglomeration process utilized within the pharmaceutical industry. Most wet granulation procedures follow some basic steps; the active agent(s) and excipients are mixed together, and a binder solution is prepared and added to the powder mixture to form a wet mass. The moist particles are then dried and sized by milling or by screening through a sieve. In some cases, the wet granulation is "wet milled" or sized through screens before the drying step. The wet granulation process may be a high shear granulation process or a fluid bed granulation process. Several methods of granulation are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety.

After granulation and drying of the resultant particles, batches are characterized with respect to properties such as final Loss on Drying (LOD), bulk density, tap density, and particle size. LOD typically is determined after each granulation using the Moisture Analyzer. Several 1 g samples may be taken and loaded into the moisture analyzer. The samples may be run for 5 minutes at a temperature of 105° C. In another embodiment, samples are run at 105° C. until there is no weight fluctuation in order to determine the LOD.

Bulk and tap densities may be determined as follows. A graduated cylinder is filled with a certain amount of material (30-40 g or 82-88 g), and the volume recorded to determine the material bulk density. Tap density can be determined with a help of a Tap Density Tester by exposing the material to 100 taps per test and recording the new volume.

Particle size determination generally is performed immediately after granulation, after sieving through 20 mesh screen to remove agglomerates. Particle diameter may be determined with a sieve-type particle diameter distribution

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gauge using sieves with openings of 30, 40, 60, 80, 120, and 325 mesh. Fractions may be weighed on a Mettler balance to estimate size distribution. This provides determination of the quantitative ratio by particle diameter of composition comprising extended release particles. Sieve analysis according to standard United States Pharmacopoeia methods (e.g., USP-23 NF 18), may be done such as by using a Meinzer II Sieve Shaker.

In one embodiment, the method for preparing dosage forms of the pharmaceutical composition may comprise wet granulating a first mixture comprising the opioid, the API, and a binder to produce a first granulation mixture. The wet granulation process may be a fluid bed granulation process. In additional embodiments, the first mixture may further comprise at least one additional excipient selected from the group consisting of fillers, lubricants, antioxidants, chelating agents, and color agents. The first granulation mixture may be blended with an extended release polymer and one or more excipients, as listed above, to form at least one extended release portion of a dosage form. In another embodiment, the extended release polymer may be a polyethylene oxide.

In another embodiment, the method further comprises wet granulating a second mixture comprising the opioid, the API, and a binder to form a second granulation mixture. The wet granulation process may be a fluid bed granulation process. In some embodiments, the second mixture may further comprise at least one additional excipient selected from the group consisting of fillers, lubricants, disintegrants, antioxidants, chelating agents, and color agents. The second granulation mixture may be blended with one or more excipients, as listed above, to form at least one immediate release portion of a dosage form.

In an additional embodiment, the method may further comprise compressing the at least one extended release portion and the at least one immediate release portion into a tablet. The tablet may be a bilayer tablet. The tablet may be coated with a tablet coating.

In another embodiment, the method may comprise granulating via a high shear wet granulation process a mixture comprising the opioid and at least one excipient to form opioid particles. The opioid particles may be dried at a suitable temperature. The opioid particles may be granulated via a fluid bed granulation process with the API, a binder, and an optional excipient to form a first granulation mixture. The first granulation mixture may be blended with an extended release polymer and at least one excipient to form an extended release portion of a solid dosage form.

In a further embodiment, the method may further comprise granulating via a fluid bed granulation process opioid particles with the API, a binder, and an optional excipient to form a second granulation mixture. The second granulation mixture may be blended with one or more excipients to form an immediate release portion of a solid dosage form.

In an additional embodiment, the method may further comprise compressing the at least one extended release portion comprising opioid particles and the at least one immediate release portion comprising opioid particles into a tablet. In one embodiment, the method comprises compressing one extended release portion comprising opioid particle and one immediate release portion comprising opioid particles into a bilayer tablet. The tablet may be coated with a tablet coating.

In another embodiment, wet granulation of either mixture may produce particles with a bulk density ranging from about 0.30 to 0.40 grams/milliliter (g/mL). In other aspects, the wet granulation may produce particles with a tap density ranging from about 0.35 g/mL to about 0.45 g/mL. In other embodiments, the wet granulation may produce particles, wherein at

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least about 50% of the particles have a size greater than 125 microns. In still other embodiments, the wet granulation may produce particles wherein about 20% to about 65% of the particles have a size greater than about 125 microns and less than about 250 microns.

Tablets generally are characterized with respect to disintegration and dissolution release profiles as well as tablet hardness, friability, and content uniformity.

In vitro dissolution profiles for the tablets may be determined using a USP Type II apparatus, at a paddle speed of about 150 rpm, in 0.1 N HCl, at 37° C. Samples of 5 mL at each time-point, may be taken without media replacement at 0.8, 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hours, for example. In some embodiments, the dissolution profiles may be determined at varying pH values, such as at a pH of about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 or 6.5. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. The resulting cumulative dissolution profiles for the tablets are based upon a theoretical percent active added to the pharmaceutical compositions.

A tablet preferably disintegrates before it dissolves. A disintegration tester measures the time it takes a tablet to break apart in solution. The tester suspends tablets in a solution bath for visual monitoring of the disintegration rate. Both the time to disintegration and the disintegration consistency of all tablets may be measured. The disintegration profile may be determined in a USP Disintegration Tester in pH 5.8 phosphate buffer or 0.1 N HCl of pH 1.2. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. Samples, 1-5 mL at each time-point, may be taken, for example, without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profiles are based upon a theoretical percent active added to the pharmaceutical compositions.

After tablets are formed by compression, it is desired that the tablets have a strength of at least 9-25 Kiloponds (kp), preferably at least about 12-20 (kp). A hardness tester generally is used to determine the load required to diametrically break the tablets (crushing strength) into two equal halves. The fracture force may be measured using a Venkel Tablet Hardness Tester, using standard USP protocols.

Friability is a well-known measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability properties are especially important during any transport of the dosage form as any fracturing of the final dosage form may result in a subject receiving less than the prescribed medication. Friability may be determined using a Roche Friability Drum according to standard USP guidelines which specifies the number of samples, the total number of drum revolutions, and the drum rpm to be used. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability.

The prepared tablets generally are tested for content uniformity to determine if they meet the pharmaceutical requirement of an acceptance value of 15 or less. Each tablet is placed in a solution of 60% methanol/40% isopropanol and stirred at room temperature until the tablet disintegrates. The solution containing the dissolved tablet generally is further diluted in 90% water/10% isopropanol/0.1% heptafluorobutyric acid and analyzed by HPLC.

IV. Methods for Administering a Gastric Retentive Pharmaceutical Composition

A further aspect of the disclosure encompasses a method for administering a gastric retentive pharmaceutical compo-

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sition comprising at least one opioid disclosed herein to a subject in need thereof. The method comprises orally administering an effective amount of the gastric retentive pharmaceutical composition to the subject, wherein the subject is in a fasted state. Moreover, upon administration of the pharmaceutical composition, the opioid in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

The subject in need thereof may be suffering from pain or diagnosed with a condition associated with pain. Suitable pain conditions are detailed below. In some embodiments, the subject may be suffering from or diagnosed with chronic pain. In yet another embodiment, the subject may be suffering from or diagnosed with acute pain. In yet other embodiments, the subject may be suffering from or diagnosed with both chronic and acute pain. The subject may be a mammal, and preferably the subject may be a human.

The gastric retentive pharmaceutical composition generally is administered to a subject in a fasted state. A fasted state may be defined as not having ingested food for at least 10 hours prior to administration of the pharmaceutical composition. In some embodiments, the subject may have fasted for at least 10 hours prior to the first dose and refrains from ingesting food for at least one hour prior to administration of subsequent doses. In other embodiments, the fasted subject may not have ingested food for at least 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours prior to administration of each dose of the pharmaceutical composition.

An effective amount of the pharmaceutical composition may comprise from about 5 mg to about 300 mg of the opioid and from about 100 mg to about 1300 mg of the other API. In embodiments in which the opioid is oxycodone and the API is acetaminophen, the pharmaceutical composition may comprise from about 7.5 mg to about 30 mg of oxycodone and from about 250 mg to about 1300 mg of acetaminophen. In one exemplary embodiment, an effective amount of the pharmaceutical composition may comprise 15 mg of oxycodone and 650 mg of acetaminophen, wherein one solid dosage form comprising 15 mg of oxycodone and 650 mg of acetaminophen is administered. In another exemplary embodiment, effective amount of the pharmaceutical composition may comprise about 15 mg of oxycodone and about 650 mg of acetaminophen, wherein two solid dosage forms each comprising 7.5 mg of oxycodone and 325 mg of acetaminophen is administered. In still another exemplary embodiment, an effective amount of the pharmaceutical composition may comprise 7.5 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 7.5 mg of oxycodone and 325 mg of acetaminophen is administered. In yet another embodiment, the effective amount of a pharmaceutical composition may be 20 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 20 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 10 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 10 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 10 mg of oxycodone and 325 mg of acetaminophen may be administered. In still yet another embodiment, the effective amount of a pharmaceutical composition may be 30 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 30 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage

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forms with each comprising 15 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 15 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 15 mg of oxycodone and 325 mg of acetaminophen may be administered.

The dosing intervals of the effective amount of the pharmaceutical composition can and will vary. For example, an effective amount of the pharmaceutical composition may be administered once a day, twice a day, or three times a day. In one embodiment, an effective amount of the pharmaceutical composition may be administered twice a day.

The pharmacokinetic parameter of the active agent(s) of the pharmaceutical composition that differs by less than about 30% under fed and fasted conditions may be, but is not limited to, C_{max}, C_{1hr}, C_{2hr}, AUC, partial AUC, T_{max}, and T_{lag}. In various embodiments, the pharmacokinetic parameter may vary by less than about 25%, 20%, 15%, 10%, or 5% under fed and fasted conditions.

In embodiments in which the pharmaceutical composition comprises oxycodone and acetaminophen, the C_{max} or AUC of oxycodone and the C_{max} or AUC of acetaminophen may each individually vary by less than about 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% under fed and fasted conditions.

Suitable pain conditions for which the subject in need may be suffering from or diagnosed with include without limitation headache pain, pain associated with migraine, neuropathic pain selected from the group consisting of diabetic neuropathy, HIV sensory neuropathy, post-herpetic neuralgia, post-thoracotomy pain, trigeminal neuralgia, radiculopathy, neuropathic pain associated with chemotherapy, reflex sympathetic dystrophy, back pain, peripheral neuropathy, entrapment neuropathy, phantom limb pain, and complex regional pain syndrome, dental pain, pain associated with a surgical procedure and or other medical intervention, bone cancer pain, joint pain associated with psoriatic arthritis, osteoarthritic pain, rheumatoid arthritic pain, juvenile chronic arthritis associated pain, juvenile idiopathic arthritis associated pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome) associated pain), pain associated with psoriatic arthritis, gout pain, pain associated with pseudogout (pyrophosphate arthritis), pain associated with systemic lupus erythematosus (SLE), pain associated with systemic sclerosis (scleroderma), pain associated with Behcet's disease, pain associated with relapsing polychondritis, pain associated with adult Still's disease, pain associated with transient regional osteoporosis, pain associated with neuropathic arthropathy, pain associated with sarcoidosis, arthritic pain, rheumatic pain, joint pain, osteoarthritic joint pain, rheumatoid arthritic joint pain, juvenile chronic arthritis associated joint pain, juvenile idiopathic arthritis associated joint pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome) associated joint pain), gout joint pain, joint pain associated with pseudogout (pyrophosphate arthritis), joint pain associated with systemic lupus erythematosus (SLE), joint pain associated with systemic sclerosis (scleroderma), joint pain associated with Behcet's disease, joint pain associated with relapsing polychondritis, joint pain associated with adult Still's disease, joint pain associated with transient regional osteoporosis, joint pain associated with neuropathic arthropathy, joint pain associated with sarcoidosis, arthritic joint pain, rheumatic joint pain, acute pain, acute joint pain, chronic pain, chronic joint pain, inflammatory pain, inflammatory

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joint pain, mechanical pain, mechanical joint pain, pain associated with the fibromyalgia syndrome (FMS), pain associated with polymyalgia rheumatica, monarticular joint pain, polyarticular joint pain, nociceptive pain, psychogenous pain, pain of unknown etiology, pain mediated by IL-6, IL-6 soluble receptor, or IL-6 receptor, pain associated with a surgical procedure in a patient with a clinical diagnosis of OA, pain like static allodynia, pain like dynamic allodynia, and/or pain associated with Crohn's disease.

It is to be understood that any ranges, ratios and ranges of ratios that can be formed by, or derived from, any of the data disclosed herein represent further embodiments of the present disclosure and are included as part of the disclosure as though they were explicitly set forth. This includes ranges that can be formed that do or do not include a finite upper and/or lower boundary. Accordingly, a person of ordinary skill in the art most closely related to a particular range, ratio or range of ratios will appreciate that such values are unambiguously derivable from the data presented herein.

Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

EXAMPLES

The following examples are included to demonstrate certain embodiments of the invention. Those of skill in the art should, however, in light of the present disclosure, appreciate that modifications can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth is to be interpreted as illustrative and not in a limiting sense.

Example 1

In Vitro Dissolution of Controlled-Release Bilayer Tablets

Controlled-release bilayer tablets were prepared containing 15 mg of oxycodone and 500 mg of acetaminophen (APAP), or 30 mg of oxycodone and 500 mg APAP. (See selected examples from Chart No. 3.) The ER layer contained 75% of the total amount of oxycodone in the tablet, 50% of the total amount of APAP in the tablet, and either 35% w/w POLYOX® 1105 (for fast release), 45% w/w POLYOX® 1105 (for medium release), or 45% w/w POLYOX® N60K (for slow release). The IR layer contained 25% of the total amount of oxycodone in the tablet and 50% of the total amount of APAP in the tablet.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel that contained 900 mL of (helium sparged) 0.1 N HCl that was heated to 37° C. ± 0.5° C. The mixture was stirred at 150 ± 6 rpm and the temperature was maintained at 37° C. ± 0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release of oxycodone and APAP from 15 mg oxycodone/500 mg APAP tablets is presented in Table 1. Table 2 presents the cumulative release of oxycodone and APAP from 30 mg oxycodone/500 mg APAP (30/500) tablets. FIG. 1 presents the release profile of oxycodone from the

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15/500 and 30/500 tablets. The dissolution profile of APAP from the 15/500 and 30/500 tablets is shown in FIG. 2. The release of oxycodone and APAP from the fast release and medium release tablets was essentially linear during the first half of the 12 hour time period but then plateaued during the last half of the 12 hour time period. The release of oxycodone and APAP from the slow release tablets was essentially linear during the entire 12 hour time period.

TABLE 1

Cumulative Release-15 mg oxycodone/500 mg APAP Tablets						
Time (hr)	Oxycodone (%)			APAP (%)		
	Fast	Medium	Slow	Fast	Medium	Slow
0.25	27.56	25.70	25.68	54.78	53.06	53.01
0.5	34.33	31.31	30.39	57.55	55.73	54.89
1.0	—	40.85	37.81	—	60.03	58.03
2.0	59.88	55.67	49.50	71.42	68.16	63.27
4.0	83.46	77.94	67.43	86.17	81.55	72.31
6.0	97.48	92.12	80.53	96.19	91.62	79.97
8.0	101.26	99.26	90.20	100.16	96.96	86.06
12.0	101.57	101.23	99.36	100.10	99.16	94.41

TABLE 2

Cumulative Release-30 mg oxycodone/500 mg APAP Tablets						
Time (hr)	Oxycodone (%)			APAP (%)		
	Fast	Medium	Slow	Fast	Medium	Slow
0.25	31.65	30.27	29.78	54.17	52.97	52.97
0.5	37.55	35.91	34.42	56.96	55.64	54.97
1.0	47.18	45.21	41.12	61.81	60.19	58.15
2.0	62.51	59.63	52.40	70.60	68.04	63.61
4.0	84.72	80.44	70.01	85.28	81.56	73.04
6.0	96.97	93.98	82.49	94.57	91.42	80.94
8.0	100.23	99.63	91.78	97.91	96.48	87.26
12.0	100.57	101.13	99.60	98.09	98.14	95.25

The cumulative in vitro release of oxycodone and APAP from 7.5 mg oxycodone/325 mg APAP medium release tablets is presented in Table 3. The ER layer of these tablets contained 5.625 mg of oxycodone, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105, and the IR layer contained 1.875 mg of oxycodone and 162.5 mg of APAP. (See selected example from Chart 2.) The dissolution profile was determined essentially as described above, except that samples were collected at 0.08 hour (~5 min) in addition to the later time points.

TABLE 3

Cumulative Release 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Oxycodone (%)		APAP (%)	
	Mean (%)	% RSD (6)	Mean (%)	% RSD (%)
0.08	26.6	4.3	49.0	3.4
0.25	31.5	4.2	51.3	3.1
0.5	37.5	2.7	53.8	2.9
1.0	45.9	1.6	58.2	2.5
2.0	60.1	1.7	66.0	2.3
4.0	81.4	1.1	78.7	1.7
6.0	95.4	1.4	88.4	1.9
8.0	101.8	0.9	93.9	1.4
12.0	103.2	1.2	94.9	1.1

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FIG. 3 and FIG. 4 present the percentage of oxycodone and APAP, respectively, released from two different lots of 7.5/325 tablets as compared to 15/650 tablets (see Example 30 for the dissolution data of the 15 mg oxycodone/650 acetaminophen tablets). The dissolution profiles were similar among all the tablets.

The release of oxycodone and APAP from each layer was analyzed by determining the calculated release from the ER layer and actual release from the total composition. For this, the tablets contained 7.5 mg of oxycodone HCl and 325 mg of APAP (i.e., the ER layer contained 5.625 mg of oxycodone HCl, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105; and the IR layer contained 1.875 mg of oxycodone HCl and 162.5 mg of APAP). The dissolution profile was determined essentially as described above. The calculated cumulative release of oxycodone HCl from the ER layer and the total tablet is presented in Table 4, and the calculated cumulative release of APAP from the ER layer and the total tablet is presented in Table 5. These data show that essentially all of the 1.875 mg of oxycodone HCl in the IR layer was released within about 5 minutes and essentially all of the 162.5 mg of APAP in the IR layer was released within about 15 minutes.

TABLE 4

Split Release of Oxycodone 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
0.08	26.6	2.00	2.1	0.12
0.25	31.5	2.36	8.7	0.49
0.5	37.5	2.81	16.7	0.94
1.0	45.9	3.44	27.9	1.57
2.0	60.1	4.51	46.8	2.63
4.0	81.4	6.11	75.2	4.23
6.0	95.4	7.16	93.9	5.28
8.0	101.8	7.64	102.4	5.76
12.0	103.2	7.74	104.3	5.87

TABLE 5

Split Release of APAP 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
0.08	49.0	159.25	0.0	0.00
0.25	51.3	166.73	2.6	4.22
0.5	53.8	174.85	7.6	12.35
1.0	58.2	189.15	16.4	26.65
2.0	66.0	214.50	32.0	52.00
4.0	78.7	255.78	57.4	93.28
6.0	88.4	287.30	76.8	124.80
8.0	93.9	305.18	87.8	142.68
12.0	94.9	308.43	89.8	145.93

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Example 2

Clinical Pharmacokinetic Analysis of
Controlled-Release 15 mg Oxycodone/500 mg
Acetaminophen Bilayer Tablets—Single Dose

An open-label, single dose, four-period crossover study was conducted to evaluate the pharmacokinetics (PK) and bioavailability of three controlled-release bilayer tablets comprising 15 mg oxycodone (OC) and 500 mg APAP as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen. The three controlled release formulations—fast, medium, and slow—described above. (See selected examples from Chart No. 3.) One tablet of each of the controlled-release bilayer formulations was administered to the test subjects under fed conditions. One tablet of the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen was administered every 6 hours (Q6h) for two doses under fed conditions. The test subjects were about 40 normal, healthy male subjects between 21-45 years of age.

Subjects were randomly assigned to Treatments A, B, C, and D using a four-period, eight-sequence, crossover design as follows:

Treatment A: One (1) tablet of 15 mg OC/500 mg APAP, Fast Release administered orally under fed conditions.

Treatment B: One (1) tablet of 15 mg OC/500 mg APAP, Medium Release administered orally under fed conditions.

Treatment C: One (1) tablet of 15 mg OC/500 mg APAP, Slow Release administered orally under fed conditions.

Treatment D: One (1) tablet of a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg administered orally Q6h for two (2) doses under fed conditions.

The crossover design allowed for within-subject comparisons among the test formulations with differing release profiles. Subjects received each of the study drug treatments (A-D) separated by at least a 7-day interval between the start of each period at Hour 0. During each period, subjects remained in the clinical facility from the time of check-in (on the day prior to dosing) until discharge on Day 3 (after the 48 hour blood draw).

Physical examinations, electrocardiograms and clinical laboratory tests were performed at screening and at the conclusion of the study (or early termination). Vital sign measurements (including pulse oximetry) and adverse events were monitored during the study. Subjects were administered a 50 mg naltrexone tablet 12 hours prior to Hour 0 dosing, at Hour 0, and 12 hours post-dose to block the effects and potential risks of oxycodone. After a 10 hour overnight fast, subjects were served a standardized FDA high-fat breakfast to be consumed in 30 minutes or less prior to Hour 0 dosing for the first oral dosage. All subjects in each period were served a standardized meal to be consumed in 30 minutes or less prior to Hour 6. Only subjects randomized to Treatment D were administered the second oral dosage of the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen at Hour 6 in each period.

Blood was drawn at designated times for PK analysis. Samples (6 mL in pre-chilled vacuum blood collection tubes, containing K2EDTA as the anticoagulant) were taken pre-dose (up to 60 minutes prior to dose), 10 min, 20 min, 30 min, 40 min and 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36 and 48 hours post-dose. The collected plasma samples were analyzed for the active pharmaceutical ingredients

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(APIs), i.e., oxycodone and acetaminophen, using validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays.

The following PK parameters were calculated for oxycodone and acetaminophen using standard non-compartmental methods:

area under the plasma concentration curve to last quantifiable concentration $AUC_{(0-t)}$

area under the plasma concentration curve to infinite time $AUC_{(0-inf)}$

maximum observed plasma concentration (C_{max})

time observed maximum plasma concentration (t_{max})

lag time (t_{lag})

apparent first-order terminal elimination rate constant (k_{el})

apparent plasma terminal elimination half-life ($t_{1/2}$)

Parametric general linear model (GLM) methodology was used in the analysis of all pharmacokinetic parameters. The SAS GLM procedure was used to perform analysis of variance (ANOVA) on each pharmacokinetic parameter with sequence, treatment, period, and subjects nested within sequences, as sources of variation. For each formulation, least squares means and the associated standard errors were obtained using the LSMEANS option. All treatment pairwise comparisons were performed, without adjustment for multiplicity. AUC and C_{max} were dose-adjusted for comparative purposes for acetaminophen and the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen.

The pharmacokinetic data for oxycodone and APAP are presented in Tables 6-8 and 9-11, respectively.

TABLE 6

Oxycodone Pharmacokinetics (15/500)					
Parameter	Fast Release Formulation				Commercially- available immediate- release tablet
	Mean	LSM	90% CI		Mean (% CV)
	(% CV)	Ratio	Lower	Upper	
C_{max} (ng/mL)	18.803 (21)	82.92	78.02	88.12	22.428 (20)
C_{1hr} (ng/mL)	6.891 (77)	72.79	49.02	108.1	10.226 (65)
C_{2hr}^a (ng/mL)	12.355 (32)	80.74	71.2	91.56	14.94 (26)
AUC_{0-t} (ng · hr/mL)	209.949 (26)	89.73	86.52	93.06	229.788 (22)
AUC_{0-inf} (ng · hr/mL)	211.8 (25)	89.95	86.77	93.24	231.421 (22)
AUC_{0-1hr} (ng · hr/mL)	2.565 (104)	61.32	37.64	99.92	4.334 (80)
AUC_{0-2hr}^b (ng · hr/mL)	12.189 (53)	70.16	55.97	87.95	16.917 (46)
AUC_{0-4hr}^c (ng · hr/mL)	41.3 (29)	88.76	80.61	97.73	45.699 (24)
T_{max} (hr)	4.954 (34)	na	na	na	7.954 (22)
T_{lag} (hr)	0.31 (68)	na	na	na	0.219 (77)
$T_{1/2}$ (hr)	4.584 (17)	na	na	na	4.495 (14)
K_{el} (1/hr)	0.155 (16)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet
^bAUC from zero to the median T_{max} for commercially-available immediate release tablet

^cAUC from the zero to the median $T_{max} + 2$ SD for commercially-available immediate release tablet

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TABLE 7

Oxycodone Pharmacokinetics (15/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	18.266 (25)	80.87	76.09	85.95	22.428 (20)
C_{1hr} (ng/mL)	7.364 (81)	67.62	45.75	99.95	10.226 (65)
C_{2hr}^a (ng/mL)	12.388 (45)	79.04	69.69	89.64	14.94 (26)
AUC_{0-t} (ng · hr/mL)	217.188 (23)	94.19	90.82	97.68	229.788 (22)
AUC_{0-inf} (ng · hr/mL)	218.545 (23)	94.09	90.77	97.54	231.421 (22)
AUC_{0-1hr} (ng · hr/mL)	3.248 (118)	64.69	39.93	104.8	4.334 (80)
AUC_{0-2hr}^b (ng · hr/mL)	13.124 (70)	71.74	57.22	89.96	16.917 (46)
AUC_{0-4hr}^c (ng · hr/mL)	42.101 (43)	88.61	80.47	97.58	45.699 (24)
T_{max} (hr)	5.31 (38)	na	na	na	7.954 (22)
T_{lag} (hr)	0.264 (64)	na	na	na	0.219 (77)
$T_{1/2}$ (hr)	4.557 (16)	na	na	na	4.495 (14)
K_{el} (1/hr)	0.156 (16)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 8

Oxycodone Pharmacokinetics (15/500)						
Parameter	Slow Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{max} (ng/mL)	17.403 (25)	76.75	72.21	81.58	22.428 (20)	
C_{1hr} (ng/mL)	7.601 (79)	69.63	47.08	102.97	10.226 (65)	
C_{2hr}^a (ng/mL)	11.237 (39)	73.55	64.84	83.43	14.94 (26)	
AUC_{0-t} (ng · hr/mL)	222.096 (25)	95.62	92.2	99.18	229.788 (22)	
AUC_{0-inf} (ng · hr/mL)	223.553 (25)	95.61	92.22	99.11	231.421 (22)	
AUC_{0-1hr} (ng · hr/mL)	2.893 (112)	57.34	35.37	92.95	4.334 (80)	
AUC_{0-2hr}^b (ng · hr/mL)	12.312 (66)	68.63	54.72	86.08	16.917 (46)	
AUC_{0-4hr}^c (ng · hr/mL)	38.842 (35)	83.46	75.78	91.92	45.699 (24)	
T_{max} (hr)	5.655 (27)	na	na	na	7.954 (22)	
T_{lag} (hr)	0.299 (74)	na	na	na	0.219 (77)	
$T_{1/2}$ (hr)	4.647 (19)	na	na	na	4.495 (14)	

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TABLE 8-continued

Oxycodone Pharmacokinetics (15/500)					
Parameter	Slow Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		
	(% CV)	Ratio	Lower	Upper	(% CV)
K _{el} (1/hr)	0.154 (18)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 9

Acetaminophen Pharmacokinetics (15/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet*
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2612 (26)	94.46	87.25	102.26	2721 (22)
C_{1hr} (ng/mL)	1627 (66)	113.22	84.91	150.98	1516 (58)
C_{2hr}^a (ng/mL)	2248 (30)	118.49	107.61	130.48	1841 (20)
AUC_{0-t} (ng · hr/mL)	21944 (27)	98.78	95.91	101.75	21962 (22)
AUC_{0-inf} (ng · hr/mL)	23090 (27)	98.73	95.85	101.7	23104 (21)
AUC_{0-1hr} (ng · hr/mL)	823 (96)	105.42	68.75	161.64	814 (82)
AUC_{0-2hr}^b (ng · hr/mL)	2761 (52)	106.73	86.55	131.62	2492 (47)
AUC_{0-4hr}^c (ng · hr/mL)	7006 (28)	119.91	110.42	130.2	5726 (22)
T_{max} (hr)	2.328 (58)	na	na	na	6.971 (34)
T_{lag} (hr)	0.276 (81)	na	na	na	0.219 (98)
$T_{1/2}$ (hr)	5.235 (35)	na	na	na	6.461 (66)
K_{el} (1/hr)	0.145 (28)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 10

Acetaminophen Pharmacokinetics (15/500)					Commercially- available immediate release tablet*
Parameter	Medium Release Formulation			Mean (% CV)	
	Mean (% CV)	LSM Ratio	90% CI Lower Upper		
C_{max} (ng/mL)	2720 (22)	99.19	91.61 107.39	2721 (22)	

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TABLE 10-continued

Acetaminophen Pharmacokinetics (15/500)					
Parameter	Medium Release Formulation				Commercially- available immediate release tablet*
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C _{1hr} (ng/mL)	1831 (54)	121.62	91.51	161.65	1516 (58)
C _{2hr} ^a (ng/mL)	2170 (23)	116.69	105.96	128.51	1841 (20)
AUC _{0-t} (ng · hr/mL)	22184 (22)	100.68	97.74	103.7	21962 (22)
AUC _{0-inf} (ng · hr/mL)	23554 (22)	101.39	98.43	104.44	23104 (21)
AUC _{0-1hr} (ng · hr/mL)	974 (85)	124.39	81.52	189.79	814 (82)
AUC _{0-2hr} ^b (ng · hr/mL)	2974 (47)	117.9	95.58	145.43	2492 (47)
AUC _{0-4hr} ^c (ng · hr/mL)	7122 (23)	123.98	114.17	134.64	5726 (22)
T _{max} (hr)	2.069 (66)	na	na	na	6.971 (34)
T _{lag} (hr)	0.218 (77)	na	na	na	0.219 (98)
T _{1/2} (hr)	5.696 (33)	na	na	na	6.461 (66)
K _{el} (1/hr)	0.133 (29)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 11

Acetaminophen Pharmacokinetics (15/500)						
Parameter	Slow Release Formulation				Commercially-available immediate release tablet*	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{max} (ng/mL)	2521 (18)	93.6	86.44	101.35	2721 (22)	
C_{1hr} (ng/mL)	1766 (51)	126.26	94.96	167.87	1516 (58)	
C_{2hr}^a (ng/mL)	2113 (18)	116.18	105.48	127.96	1841 (20)	
AUC_{0-t} (ng · hr/mL)	21947 (25)	99.61	96.7	102.61	21962 (22)	
AUC_{0-inf} (ng · hr/mL)	23279 (25)	100.47	97.53	103.49	23104 (21)	
AUC_{0-1hr} (ng · hr/mL)	872 (83)	115.25	75.49	175.95	814 (82)	
AUC_{0-2hr}^b (ng · hr/mL)	2811 (43)	116.49	94.42	143.73	2492 (47)	
AUC_{0-4hr}^c (ng · hr/mL)	6828 (19)	120.68	111.11	131.07	5726 (22)	
T_{max} (hr)	2.184 (59)	na	na	na	6.971 (34)	

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TABLE 11-continued

Acetaminophen Pharmacokinetics (15/500)						
5						Commercially- available immediate release tablet*
10		Slow Release Formulation				
		Mean	LSM	90% CI		Mean
15	Parameter	(% CV)	Ratio	Lower	Upper	(% CV)
	T_{lag} (hr)	0.253 (86)	na	na	na	0.219 (98)
	$T_{1/2}$ (hr)	5.366 (32)	na	na	na	6.461 (66)
20	K_{el} (1/hr)	0.141 (28)	na	na	na	0.137 (39)

25 *Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 12

Pharmacokinetic Profile (Mean ± SD) of Oxycodone/APAP versus commercially-available immediate release tablet (N = 29)							
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max} (hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)	
Oxycodone							
15 mg OC/	18.3 ± 4.6	217 ± 49.2	219 ± 49.5	5.3 ± 2.0	0.156 ± 0.024	4.6 ± 0.7	
500 mg APAP							
Commercially-available immediate release tablet	22.4 ± 4.5*	230 ± 49.8	231 ± 50.0	8.0 ± 1.7*	0.157 ± 0.020	4.5 ± 0.6	
Acetaminophen							
15 mg OC/	2720 ± 608	221184 ± 4804	23554 ± 5234	2.1 ± 1.4	0.133 ± 0.039	5.7 ± 1.9	
500 mg APAP							
Commercially-available immediate release tablet ^a	2721 ± 584*	21962 ± 4772	23104 ± 4882	7.0 ± 2.4*	0.137 ± 0.054	6.5 ± 4.3	
(7.5 mg OC/325 mg APAP)							
65 *Most values occurred after the second dose.							
^a AUC and C_{max} dose-normalized to 500 mg for APAP.							

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TABLE 13

Time Course of Oxycodone Plasma Concentration (ng/mL)								
Time (hr)	Mean Fast	SEM	Mean Medium	SEM	Mean Slow	SEM	Mean commercially-available immediate release tablet	SEM
0	0	0	0	0	0	0	0	0
0.17	0	0	0.13	0.11	0.06	0.02	0.03	0.03
0.33	0.65	0.29	1.08	0.44	0.93	0.41	1.16	0.36
0.5	2.09	0.55	2.98	0.95	2.55	0.96	4.03	0.9
0.67	3.74	0.91	5.29	1.25	4.15	1.1	7.04	0.93
1	6.89	0.98	7.36	1.11	7.6	1.24	10.23	1.11
2	12.36	0.74	12.39	1.04	11.24	0.73	14.94	0.81
3	14.77	0.82	14.73	0.91	13.35	0.53	14.84	0.62
4	16.33	0.8	16.1	0.82	15.12	0.44	12.95	0.58
5	16.28	0.67	15.89	0.81	15.83	0.41	10.58	0.8
6	17.4	0.72	16.43	0.81	15.76	0.41	9.1	0.67
6.5	16.59	0.64	15.89	0.72	15.22	0.96	10.76	0.7
7	15.28	0.58	14.83	0.69	14.49	1.43	16.84	0.69
8	14.02	0.6	14.29	0.64	13.77	0.85	19.7	0.7
9	13.13	0.57	13.39	0.55	13	0.78	19.08	0.65
10	11.9	0.64	12.52	0.53	11.92	0.68	16.63	0.57
12	8.86	0.6	9.59	0.49	10.04	0.59	10.88	0.53

TABLE 14

Time Course of Acetaminophen Plasma Concentration (ng/mL)								
Time (hr)	Mean Fast	SEM	Mean Medium	SEM	Mean Slow	SEM	Mean commercially-available immediate release tablet	SEM
0	0	0	0	0	0	0	0	0
0.17	31	18	284	151	220	88	107	47
0.33	673	210	751	221	678	197	607	173
0.5	1216	266	1299	275	1133	248	1181	229
0.67	1624	301	1922	301	1647	252	1653	255
1	2116	258	2380	239	2296	217	1971	210
2	2922	160	2821	123	2747	93	2393	90
3	2736	129	2719	90	2636	94	2150	65
4	2643	120	2524	103	2424	110	1717	71
5	2376	112	2246	121	2130	118	1290	59
6	2263	100	2080	143	1965	107	1006	58
6.5	2068	93	1903	126	1774	102	1742	212
7	1830	80	1744	116	1644	98	2749	232
8	1577	81	1573	103	1495	93	2790	114
9	1416	79	1407	88	1330	80	2482	111
10	1286	82	1314	84	1198	71	1968	105
12	1069	89	1131	86	1089	66	1188	82

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Example 3

TABLE 15

Clinical Pharmacokinetic Analysis of
Controlled-Release 30 mg Oxycodone/500 mg
Acetaminophen Bilayer Tablets—Single Dose

A single dose, four-period crossover study was conducted essentially as described in Example 2, except the controlled-release bilayer tablets contained 30 mg oxycodone and 500 mg APAP. (See selected examples from Chart No. 2.) Tables 15-17 and 18-20 present the PK data for oxycodone and APAP, respectively. The plasma concentrations of oxycodone and APAP are presented in FIG. 7 and FIG. 8, respectively.

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Oxycodone Pharmacokinetics (30/500)

Fast Release Formulation				Commercially- available immediate release tablet
Mean	LSM	90% CI		
(% CV)	Ratio	Lower	Upper	(% CV)
39.159 (28)	82.17	75.96	88.9	47.597 (26)
20.462 (74)	77.25	54.37	109.76	25.911 (67)
28.221 (39)	95.18	83.82	108.08	29.579 (32)

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TABLE 15-continued

Oxycodone Pharmacokinetics (30/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
AUC _{0-t} (ng · hr/mL)	393.952 (30)	92.84	89.3	96.53	425.978 (29)
AUC _{0-inf} (ng · hr/mL)	396.135 (29)	92.4	88.94	95.99	430.196 (29)
AUC _{0-1hr} (ng · hr/mL)	9.106 (100)	71.09	46.05	109.76	11.55 (93)
AUC _{0-2hr^b} (ng · hr/mL)	33.448 (61)	82.59	67.9	100.46	39.295 (53)
AUC _{0-4hr^c} (ng · hr/mL)	96.47 (38)	101.27	91.51	112.06	93.706 (29)
AUC _{4hr-t^d} (29)	395.522 (29)	92.4	88.95	95.99	429.507 (29)
T _{max} (hr)	4.057 (51)	na	na	na	6.948 (33)
T _{lag} (hr)	0.213 (107)	na	na	na	0.184 (66)
T _{1/2} (hr)	4.398 (15)	na	na	na	4.32 (15)
K _{el} (1/hr)	0.161 (15)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 16

Oxycodone Pharmacokinetics (30/500)					
Parameter	Medium Release Formulation				Commercially- available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C _{max} (ng/mL)	36.731 (30)	77.14	71.27	83.48	47.597 (26)
C _{1hr} (ng/mL)	19.758 (70)	86.12	60.48	122.62	25.911 (67)
C _{2hr} ^a (ng/mL)	27.655 (39)	93.53	82.31	106.28	29.579 (32)
AUC _{0-t} (ng · hr/mL)	396.026 (29)	94.17	90.55	97.92	425.978 (29)
AUC _{0-inf} (ng · hr/mL)	398.084 (29)	93.68	90.16	97.34	430.196 (29)
AUC _{0-1hr} (ng · hr/mL)	8.988 (85)	93.06	60.12	144.04	11.55 (93)
AUC _{0-2hr} ^b (ng · hr/mL)	32.695 (56)	86.02	70.64	104.74	39.295 (53)
AUC _{0-4hr} ^c (ng · hr/mL)	91.998 (36)	98.13	88.63	108.65	93.706 (29)
AUC _{4hr-t} ^d (29)	397.436 (29)	93.68	90.16	97.34	429.507 (29)
T _{max} (hr)	4.523 (51)	na	na	na	6.948 (33)
T _{lag} (hr)	0.207 (95)	na	na	na	0.184 (66)
T _{1/2} (hr)	4.369 (14)	na	na	na	4.32 (15)

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TABLE 16-continued

Oxycodone Pharmacokinetics (30/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		
	(% CV)	Ratio	Lower	Upper	(% CV)
K _{el} (1/hr)	0.162 (14)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet

^bAUC from zero the median T_{max} for commercially-available immediate release tablet

^cAUC from the zero to the median T_{max} + 2 SD for commercially-available immediate release tablet

TABLE 17

20	Oxycodone Pharmacokinetics (30/500)					
						Commercially- available immediate release tablet
25	Slow Release Formulation					
	Mean	LSM	90% CI		Mean	
	Parameter	(% CV)	Ratio	Lower	Upper	(% CV)
30	C _{max} (ng/mL)	32.976 (29)	68.96	63.74	74.6	47.597 (26)
	C _{1hr} (ng/mL)	17.897 (74)	73.61	52.01	104.18	25.911 (67)
	C _{2hr} ^a (ng/mL)	23.183 (33)	78.42	69.06	89.05	29.579 (32)
	AUC _{0-t} (ng · hr/mL)	399.623 (26)	94.5	90.9	98.25	425.978 (29)
35	AUC _{0-inf} (ng · hr/mL)	401.362 (26)	93.88	90.36	97.52	430.196 (29)
	AUC _{0-1hr} (ng · hr/mL)	7.643 (96)	69.93	45.52	107.44	11.55 (93)
	AUC _{0-2hr} ^b (ng · hr/mL)	28.183 (59)	71.58	58.85	87.06	39.295 (53)
40	AUC _{0-4hr} ^c (ng · hr/mL)	82.171 (36)	86.17	77.87	95.35	93.706 (29)
	AUC _{4hr-t} ^d (26)	400.56 (26)	93.85	90.34	97.49	429.507 (29)
45	T _{max} (hr)	3.96 (48)	na	na	na	6.948 (33)
	T _{lag} (hr)	0.201 (78)	na	na	na	0.184 (66)
	T _{1/2} (hr)	4.418 (17)	na	na	na	4.32 (15)
	K _{el} (1/hr)	0.161 (17)	na	na	na	0.164 (16)

TABLE 18

Acetaminophen Pharmacokinetics (30/500)						
60	Fast Release Formulation				Commercially- available immediate release tablet	
	Mean	LSM	90% CI			Mean
	Parameter	(% CV)	Ratio	Lower		Upper
65	C _{max} (ng/mL)	3138 (32)	101.52	91.58	122.53	3085 (29)

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TABLE 18-continued

Acetaminophen Pharmacokinetics (30/500)						
Parameter	Fast Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{1hr} (ng/mL)	2163 (59)	130.98	101.04	169.78	1777 (59)	
C_{2hr}^a (ng/mL)	2386 (32)	125.37	113.22	138.82	1892 (28)	
AUC_{0-t} (ng · hr/mL)	21742 (26)	98.53	95.07	102.13	21897 (23)	
AUC_{0-inf} (ng · hr/mL)	22798 (26)	99.02	95.5	102.66	22881 (23)	
AUC_{0-1hr} (ng · hr/mL)	1260 (85)	122.71	85.05	177.03	1005 (80)	
AUC_{0-2hr}^b (ng · hr/mL)	3534 (53)	120.52	100.69	144.26	2839 (48)	
AUC_{0-4hr}^c (ng · hr/mL)	8038 (33)	130.54	119.98	142.02	6041 (27)	
AUC_{4hr-t}^d (hr)	14707 (32)	86.22	82.35	90.27	16720 (26)	
T_{max} (hr)	1.908 (69)	na	na	na	5.615 (54)	
T_{lag} (hr)	0.236 (106)	na	na	na	0.178 (90)	
$T_{1/2}$ (hr)	4.798 (26)	na	na	na	5.3 (43)	
K_{el} (1/hr)	0.153 (25)	na	na	na	0.152 (36)	

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median $T_{max} + 2$ SD for commercially-available immediate release tablet

TABLE 19

Acetaminophen Pharmacokinetics (30/500)					
	Medium Release Formulation				Com- mercially- available immediate release tablet
Para-	Mean	LSM	90% CI		Mean
meter	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2940 (38)	93.8	84.57	104.03	3085 (29)
C_{1hr} (ng/mL)	2161 (56)	139.29	107.29	180.84	1777 (59)
C_{2hr}^a (ng/mL)	2349 (27)	125.86	113.61	139.44	1892 (28)
AUC_{0-t} (ng · hr/mL)	21822 (26)	99.42	95.9	103.06	21897 (23)
AUC_{0-inf} (ng · hr/mL)	23107 (26)	100.76	97.16	104.49	22881 (23)
AUC_{0-1hr} (ng · hr/mL)	1342 (81)	155.89	107.81	225.4	1005 (80)
AUC_{0-2hr}^b (ng · hr/mL)	3596 (52)	129.14	107.79	154.73	2839 (48)
AUC_{0-4hr}^c (ng · hr/mL)	7880 (32)	130.08	119.51	141.59	6041 (27)

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TABLE 19-continued

Acetaminophen Pharmacokinetics (30/500)						
Para-meter	Medium Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
AUC _{4hr-t} ^d	15040 (29)	88.93	84.92	93.13	16720 (26)	
T _{max} (hr)	1.724 (62)	na	na	na	5.615 (54)	
T _{lag} (hr)	0.19 (114)	na	na	na	0.178 (90)	
T _{1/2} (hr)	6.116 (63)	na	na	na	5.3 (43)	
K _{el} (1/hr)	.0139 (37)	na	na	na	0.152 (36)	

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median $T_{max} + 2$ SD for commercially-available immediate release tablet

TABLE 20

Acetaminophen Pharmacokinetics (30/500)						
Parameter	Slow Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
C_{max} (ng/mL)	2734 (33)	88.33	79.68	97.91	3085 (29)	
C_{1hr} (ng/mL)	1989 (53)	120.26	93.05	155.44	1777 (59)	
C_{2hr}^a (ng/mL)	2131 (25)	112.77	101.84	124.86	1892 (28)	
AUC_{0-t} (ng · hr/mL)	21272 (23)	97.1	93.68	100.64	21897 (23)	
AUC_{0-inf}^f (ng · hr/mL)	22504 (22)	98.45	94.95	102.07	22881 (23)	
AUC_{0-1hr} (ng · hr/mL)	1092 (76)	120.91	84.15	173.72	1005 (80)	
AUC_{0-2hr}^b (ng · hr/mL)	3152 (45)	112.74	94.19	134.94	2839 (48)	
AUC_{0-4hr}^c (ng · hr/mL)	7217 (26)	119.31	109.5	129.61	6041 (27)	
AUC_{4hr-t}^d (hr)	15227 (26)	90.59	86.52	94.85	16720 (26)	
T_{max} (hr)	1.897 (56)	na	na	na	5.615 (54)	
T_{lag} (hr)	0.196 (79)	na	na	na	0.178 (90)	
$T_{1/2}$ (hr)	4.843 (27)	na	na	na	5.3 (43)	
K_{el} (1/hr)	0.152 (24)	na	na	na	0.152 (36)	

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median $T_{max} + 2$ SD for commercially-available immediate release tablet

65 The pharmacokinetic parameters for the medium release 30/500 formulation and the commercially-available immediate release tablet are shown in Table 21.

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TABLE 21

Pharmacokinetic Profile (Mean \pm SD) of Oxycodone/APAP versus Commercially-available immediate release tablet (N = 29)						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max} (hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Oxycodone						
30 mg OC/500 mg APAP	36.7 \pm 10.9	396 \pm 116	398 \pm 115	4.5 \pm 2.3	0.162 \pm 0.023	4.4 \pm 0.6
Commercially-available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	47.6 \pm 12.3*	426 \pm 125	430 \pm 124	6.9 \pm 2.3*	0.164 \pm 0.026	4.3 \pm 0.6
Acetaminophen						
30 mg OC/500 mg APAP	2940 \pm 1105	21822 \pm 5630	23107 \pm 5927	1.7 \pm 1.1	0.139 \pm 0.052	6.1 \pm 3.9
Commercially-available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	3085 \pm 899*	21897 \pm 5125	22881 \pm 5362	5.6 \pm 3.0*	0.152 \pm 0.055	5.3 \pm 2.3

*Most values occurred after the second dose.

^aAUC and C_{max} dose-normalized to 30 mg for OC and 500 mg for APAP.

Example 4

Clinical Pharmacokinetic Analysis of
Controlled-Release 15 mg Oxycodone/650 mg
Acetaminophen Bilayer Tablets—Single Dose

The following study evaluated the bioavailability, pharmacokinetics, dose-proportionality, and safety of 1 or 2 tablets of a formulation comprising 15 mg OC/650 mg APAP (1 dose) (see selected example from Chart No. 1) compared to 1 tablet of the commercially-available immediate release tablet under fed conditions. The ER layer contained 75% of the total amount of the oxycodone in the tablet, 50% of the total amount of APAP in the tablet, and 45% (w/w) POLYOX® 1105. The IR layer contained 25% of the total amount of oxycodone in the tablet and 50% of the total amount of APAP. This study was conducted in 42 male and female healthy subjects.

PK parameters for oxycodone are presented in Table 22. Plasma concentrations of OC for the 1 tablet dosing configuration of 15/650 showed a median t_{lag} of 0.25 hours, while there was no lag time for plasma concentrations of OC for the 2 tablet dosing configuration of 15/650 and the commer-

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cially-available immediate release tablet under fed conditions. As illustrated in FIG. 9 demonstrating the plasma concentrations of oxycodone versus time of treatment (i.e., Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions; Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions; and Treatment C was one tablet of the commercially-available immediate release tablet (7.5 mg oxycodone/325 mg acetaminophen) administered orally every 6 hours for 2 doses under fed conditions). Plasma concentrations of OC rose rapidly after administration of 15/650 formulation in a similar fashion to commercially-available immediate release tablet. Peak plasma levels of OC for the 15/650 tablets, however, were biphasic. Peak levels were observed at about 2-3 hours and about 6 hours for the 1 or 2 tablet dosing configuration of the 15/650 formulation. In contrast, the peak plasma level of OC for the commercially-available immediate release tablet was about 7-8 hours after the initial dose of the commercially-available immediate release tablet (~1-2 hr after the second dose). Mean plasma concentrations of OC from 15/650 formulations were detectable through 48 hours following all treatments and $t_{1/2}$ was about 4 hours across all treatments.

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TABLE 22

Pharmacokinetic Parameter Estimates (Mean \pm SD) of Oxycodone Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max} ^a (hr)	T_{lag} ^a (hr)	$t_{1/2}$ (hr)
One tablet (N = 25)	17.68 (4.42)	199.60 (59.52)	201.6 (59.27)	3.00 (1.00-12.45)	0.25 (0.00 - 0.75)	4.18 (0.77)
Treatment A						
Two tablets (N = 25)	29.18 (6.53)	414.73 (109.87)	417.41 ^b (112.17)	5.00 (1.00-12.00)	0.00 (0.00-0.50)	4.11b (0.67)
Treatment B						
Commercially-available immediate release tablet (7.5 mg)	20.34 (4.81)	199.63 (60.53)	201.76 (60.24)	7.00 (0.50-9.00)	0.00 (0.00-1.00)	4.08 (0.64)

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TABLE 22-continued

Pharmacokinetic Parameter Estimates (Mean \pm SD) of Oxycodone Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
OC/325 mg APAP (N = 25) Treatment C						

^a T_{max} and t_{lag} median (minimum - maximum)^bN = 24

PK parameters for APAP are presented in Table 23. Plasma concentrations of APAP for the 1 tablet dosing configuration of 15/650 showed a median t_{lag} of 0.25 hour, while there was no lag in the appearance of APAP in plasma for the 2 tablet dosing configuration of 15/650 and the commercially-available immediate release tablet. Plasma concentrations of APAP rose rapidly after administration of the 15/650 formulations, similar to that observed with RDL. (See FIG. 10). Peak plasma levels of APAP following administration of the 1 tablet and 2 tablet dosing configurations of 15/650 were observed at approximately 2 hours (with a shoulder peak at 5-6 hours) after dosing compared with 1 hour after the second dose of the commercially-available immediate release tablet. Mean plasma concentrations of APAP were detectable through 36 hours following all treatments and the mean $t_{1/2}$ was approximately 6 to 8 hours across treatment groups.

TABLE 23

Pharmacokinetic Parameter Estimates (Mean \pm SD) of APAP Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet (N = 25)	3822 (874)	30239 (5673)	32194 ^c (6437)	2.00 (0.50-4.00)	0.25 (0.00-1.00)	6.17 ^c (2.22)
Two tablets (N = 25)	6941 (1989)	64783 (15017)	67600 ^d (14655)	2.00 (0.50-5.00)	0.00 (0.00-0.50)	7.67 ^d (4.06)
Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP) (N = 25)	3629 (841)	30137 (6426)	30802 ^c (6697)	6.50 (0.50-9.00)	0.00 (0.00-1.00)	5.89 ^c (2.63)

^a T_{max} and t_{lag} median (minimum-maximum)^bN = 21^cN = 23

Example 5

Clinical Pharmacokinetic Analysis of
Controlled-Release 15 mg Oxycodone/650 mg
Acetaminophen Bilayer Tablets—Multiple Doses

The following study evaluated the steady state bioavailability, pharmacokinetics, and safety of a 15 mg OC/650 mg APAP formulation administered (see selected example from Chart No. 2) orally as 1 tablet (Treatment A) or 2 tablets (Treatment B) every 12 hours (9 doses) compared to 2 tablets

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of the commercially-available immediate release tablet (2 \times 7.5 mg OC/325 mg APAP) (Treatment C) dosed every 6 hours for 4.5 days (18 doses) under fed conditions with 48 male and female subjects in equal distribution.

The pharmacokinetic (PK) parameters of OC are presented in Table 24. The PK behavior of OC on Study Day 1 was similar to that observed in the single dose study (see Table 22). There was a slight lag (median t_{lag} 0.25 hr) in the appearance of OC following the 1 tablet dose of 15 mg OC/650 mg APAP. No lag was observed following dosing with 2 tablets of 15 mg OC/650 mg APAP or the commercially-available immediate release tablet. Peak plasma levels were observed at 4 and 6 hours after administration of 1 and 2 tablets of the 15/650 formulation, respectively, and at 1.5 hours after the second dose of the commercially-available immediate release tablet. (See FIG. 11). Minimum (trough) plasma concentrations (C_{min}) of OC achieved steady-state levels by Day 2 for 15/650 formulations and by Day 3 for the commercially-available immediate release tablet.

TABLE 24

Oxycodone Pharmacokinetic Parameters					
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
A: One tablet Day 1 (N = 20)	18.79 (5.00)	149.68 ^c (37.92)	4.00 (2.00-8.00)	0.25 (0.00-0.50)	Day 1
B: Two tablets Day 1 (N = 20)	33.57 (8.41)	280.45 ^c (62.61)	5.93 (1.00-11.92)	0.00 (0.00-0.25)	Day 1
C: Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP) Day 1 (N = 20)	36.02 (10.52)	278.60 ^c (67.17)	7.50 (0.75-11.92)	0.00 (0.00-0.33)	Day 1
A: One tablet Day 5 (N = 20)	27.26 (6.33)	223.10 ^c (59.45)	3.00 (1.00-5.92)	Day 5	6.06 ^d (1.91)
B: Two tablets Day 5 (N = 20)	50.70 (10.95)	433.37 ^c (93.21)	3.00 (2.00-7.00)	Day 5	6.35 (1.89)
C: Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP) Day 5 (N = 20)	52.41 (12.40)	435.70 ^c (98.68)	2.00 (0.50-8.02)	Day 5	5.93 ^d (1.68)

^a T_{max} and t_{lag} median (minimum - maximum)^cDay 1 - AUC_{0-12h} ; Day 5 - AUC_{0-12h}^{ss} ^dN = 19

On Day 5 of the study, the maximum plasma OC concentration at steady-state (C_{max}^{ss}) was 27.3 ng/mL following 4.5

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days of dosing with 1 tablet of 15 mg OC/650 mg APAP administered every 12 hours. C_{max}^{ss} following 2 tablets of 15 mg OC/650 mg APAP administered every 12 hours or the commercially-available immediate release tablet administered Q6 hours for 4.5 days were 50.7 ng/mL and 52.4 ng/mL, respectively. Median T_{max}^{ss} was observed at 3 hours following 1 tablet or 2 tablets of 15/650 and at 2 hours following the first daily dose of the commercially-available immediate release tablet.

PK parameters for APAP are presented in Table 25. Acetaminophen was rapidly absorbed following a single dose of 1 or 2 tablets of 15/650 and in a similar fashion to the commercially-available immediate release tablet (see FIG. 12). There was no lag in plasma concentrations following any of the three dosing regimens. Peak APAP plasma concentrations were observed at 1 hour after administration of 1 or 2 tablets of 15/650 and at 0.9 hours after the first dose of the commercially-available immediate release tablet on Day 1. After a single administration of 15/650, C_{max} for APAP was proportional with respect to the amount of APAP in 1 or 2 tablets of 15/650 (i.e., 1 tablet—3942 ng/mL; 2 tablets—7536 ng/mL). Minimum (trough) concentrations (C_{min}) of APAP achieved steady-state levels by Day 2 for 1 tablet of 15/650, by Day 4 for 2 tablets of 15/650 and by the second dose on Day 1 for the commercially-available immediate release tablet.

TABLE 25

Acetaminophen Pharmacokinetic Parameters						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)	
A: One tablet Day 1 (N = 20)	3942 (1168)	22928 ^g (7331)	1.00 (0.50- 5.93)	0.00 (0.00- 0.28)		
B: Two tablets Day 1 (N = 20)	7536 (2205)	44254 ^g (13885)	1.00 (0.28- 4.00)	0.00 (0.00- 0.25)		
C: Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP Day 1 (N = 20)	6757 (1949)	43634 ^g (12357)	0.90 (0.32- 11.92)	0.00 (0.00- 0.25)		
A: One tablet Day 5 (N = 20)	4635 (1330)	26968 ^g (9134)	1.00 (0.50- 3.00)	Day 5 (2.24)	7.06	
B: Two tablets Day 5 (N = 20)	8206 (2666)	50221 ^g (18415)	1.00 (0.30- 4.00)	Day 5 (1.85)	7.46	
C: Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP Day 5 (N = 20)	7433 (1979)	50678 ^g (15565)	1.50 (0.25- 8.02)	Day 5 (2.47)	6.79 ^h	

^a T_{max} and t_{lag} median (minimum - maximum)

^gDay 1 - AUC_{0-12h} ; Day 5 - AUC_{0-12h}^{ss}

^hN = 17

On Day 5 of the study, median T_{max}^{ss} for APAP was observed at 1 hour following 1 or 2 tablets of 15/650 and at 1.5 hours following the first daily dose of the commercially-available immediate release tablet on Day 5. Maximum plasma APAP concentration at steady-state (C_{max}^{ss}) was 4635 ng/mL following 4.5 days of dosing with 1 tablet of 15/650 administered every 12 hours and for the commer-

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cially-available immediate release tablet administered Q6 hours for 4.5 days were 8206 and 7433 ng/mL, respectively.

Example 6

Clinical Pharmacokinetic Analysis of
Controlled-Release 15 mg Oxycodone/650 mg
Acetaminophen Bilayer Tablets Under Fed and
Fasted Conditions

Two open-label, randomized, two-period crossover studies were conducted to evaluate the effect of food on the pharmacokinetics, bioavailability and safety of the 15 mg oxycodone/650 mg APAP composition (see selected example from Chart No. 2) using a 1 tablet or 2 tablet dosing configuration in normal, healthy subjects. Studies were conducted in 48 subjects under fed (FDA high fat breakfast) or fasted conditions.

Tables 26 and 27 present the pharmacokinetic data for oxycodone (OC) and APAP, respectively. FIGS. 13 and 14 present the plasma concentration of OC following administration of one tablet and two tablets, respectively, under fed (Treatment A) or fasted (Treatment B) conditions. FIGS. 15 and 16 present the plasma concentration of APAP following administration of one tablet and two tablets, respectively, under fed (Treatment A) or fasted (Treatment B) conditions.

TABLE 26

Oxycodone Pharmacokinetics (15/650)							
Dose	State (N)	C_{max} (ng/ mL)	AUC_{0-t} (ng · hr/ mL)	AUC_{0-inf} (ng · hr/ mL)	T_{max}^a (hr)	t_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet	fed	19.03 (28)	219.23 (4.20)	221.06 (55.88)	5.00 (1.00- 12.00)	0.25 (0.00- 0.50)	3.94 (0.69)
	Two tablets	30.58 (17)	414.01 (6.57)	415.88 (104.76)	5.00 (0.75- 12.00)	0.25 (0.00- 0.27)	4.42 (0.97)
One tablet	fasted	18.31 (28)	196.51 (4.67)	198.33 (52.82)	3.50 (0.50- 10.00)	0.00 (0.00- 0.25)	4.25 (0.59)
	Two tablets	33.69 (17)	390.33 (7.45)	392.15 (145.81)	5.00 (2.00- 5.20)	0.00 (0.00- 0.25)	4.80 (1.07)

^a T_{max} and t_{lag} median (minimum - maximum)

Plasma concentrations (Table 26; FIGS. 13 and 14) of OC rose rapidly with the median T_{max} observed at about 4 to 5 hr under both fed and fasted conditions for both the 1- and 2-tablet dose configurations. OC plasma levels were biphasic—with a first peak at about 3 hours and a second peak at about 5 hours. The C_{max} values (at 5 hours) for OC under fed (1 and 2 tablets, 19.0 and 30.6 ng/mL) conditions were equivalent to those observed under fasted (1 and 2 tablets, 18.3 and 33.7 ng/mL) conditions for both the 1 tablet and 2 tablet dosing configurations.

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TABLE 27

Acetaminophen Pharmacokinetics (15/650)							
Dose	State (N)	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max}^a (hr)	t_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet	fed (28)	4374 (1286)	31480 (9316)	32552 (9489)	1.00 (0.50, 5.00)	0.00 (0.00-0.50)	4.65 (1.26)
Two tablets	fed (17)	6341 (1698)	62904 (19294)	68839b (19826)	2.00 (0.75-6.00)	0.00 (0.00-0.25)	7.02b (1.77)
One tablet	fasted (28)	5511 (2095)	31876 (103339)	33860 (10731)	0.75 (0.25, 5.00)	0.00 (0.00-0.25)	5.19e (1.50)
Two tablets	fasted (17)	10428 (3529)	61164 (16552)	6528 1(15711)	0.75 (0.25-5.00)	0.00 (0.00-0.00)	5.6 (1.49)

^a T_{max} and t_{lag} median (minimum - maximum)^bN = 12^cN = 27^dN = 13

Plasma concentrations (Table 27; FIGS. 15 and 16) of APAP rose rapidly following 1 tablet dosed under fed and fasted conditions with similar T_{max} values (1.0 hour and 0.8 hour). T_{max} was observed sooner following 2 tablets given under fasted conditions (0.8 hour) than under fed conditions (2 hours). Plasma concentrations of APAP were lower under fed conditions than under fasted conditions with fed C_{max} values of 4374 ng/mL (1 tablet) and 6341 ng/mL (2 tablets) and fasted C_{max} values of 5511 ng/mL (1 tablet) and 10,428 ng/mL (2 tablets). Nevertheless, the peak concentrations demonstrate that there was only a slight, minimal food effect on the absorption of APAP, which is consistent with that observed for other oxycodone and acetaminophen products. Thus, there is no meaningful food effect seen with this composition, and as such, the composition can be administered without regard to food.

Example 7

Abuse Potential of Controlled-Release Formulations

It has long been theorized that the desirability of a drug of abuse is related to the speed with which it reaches maximum concentration in the plasma of the user. Basic science and clinical observation suggest that a shortened time to maximum plasma concentration (t_{max}) and a heightened maximum plasma concentration (C_{max}) would increase the euphoric effects conferred by a drug. The abuse quotient (AQ) is a relatively new concept that attempts to predict the abuse potential of drugs. The AQ refers to the two PK parameters expressed as a ratio: $AQ = C_{max}/t_{max}$. The abuse potential of a drug increases as the value of the AQ increases, either by heightening C_{max} or shortening t_{max} .

Table 28 presents the AQs for various extended release formulations disclosed herein (see, e.g., selected examples from Chart Nos. 1 and 2) and several commercially available formulations.

TABLE28

Abuse Quotient			
Formulation	C_{max} (ng/mL)	t_{max} (hr)	AQ
15/500 - Fast	18.8	4.95	3.80
15/500 - Medium	18.27	5.31	3.44
15/500 - Slow	17.4	5.66	3.07

TABLE28-continued

Abuse Quotient			
Formulation	C_{max} (ng/mL)	t_{max} (hr)	AQ
15/650 - 1 tablet	17.68	3.90	4.53
15/650 - 2 tablets	14.59*	5.03	2.90
7.5/325 - 1 tablet	16.82	3.71	4.53
7.5/325 - 2 tablets	16.39	3.17	5.17
Percocet	22.43	2.16	10.38
Oxycontin	17.35	3.54	4.90
OxyER	19.61	4.11	4.77

*dose normalized to 15 mg

Example 8

Ethanol Release Testing at a 150 rpm Paddle Speed

To assess the potential for dose dumping, the in vitro dissolution of oxycodone and APAP from 7.5 mg OC/325 mg APAP tablets was tested in 0.1 N HCl containing 0%, 5%, 20%, or 40% v/v ethanol. The ER layer of the 7.5/325 tablets contained 5.625 mg of OC, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105, and the IR layer contained 1.875 mg of OC and 162.5 mg of APAP. (See selected example from Chart No. 2.) For each profile, twelve tablets were weighed, placed in a sinker, and dropped into an equilibrated USP Type II apparatus (paddles) that contained 900 mL of (helium sparged) 0.1 N HCl (containing either 0%, 5%, 20%, or 40% ethanol) heated to ~37° C. The mixture was stirred at ~150 rpm and the temperature was maintained at ~37° C. for 120 minutes. The bath vessel was covered with a low evaporation vessel cover. Samples were removed at 15, 30, 45, 60, 75, 90, 105, and 120 minutes. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

Tables 29, 30, 31, and 32 present the percent release of OC and APAP in the presence of 0%, 5%, 20%, and 40% ethanol, respectively. FIG. 17 presents dissolution profiles for OC and FIG. 18 presents dissolution profiles for APAP in the presence of 0%, 5%, 20%, and 40% ethanol. These data reveal that, for both OC and APAP, the dissolution in 5%, 20%, or 40% ethanol was either comparable or slower than the dissolution in 0% ethanol, indicating no dose dumping for this formulation.

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TABLE 29

Percent Release in 0% Ethanol								
Time (Min)	OC			APAP				
	Mean	RSD	Mini- mum	Maxi- mum	Mean	RSD	Mini- mum	Maxi- mum
15	32.0	2.7	31.1	33.4	52.9	2.7	50.6	56.0
30	37.6	2.4	36.5	39.2	55.6	2.5	53.5	58.6
45	42.3	2.6	40.9	44.4	58.1	2.5	56.0	61.1
60	46.5	2.5	45.0	48.7	60.5	2.4	58.4	63.5
75	50.4	2.5	48.7	52.5	62.9	2.4	60.8	65.9
90	54.1	2.4	52.1	56.2	65.0	2.3	62.9	68.0
105	57.7	2.1	55.6	59.8	67.1	2.3	65.0	70.1
120	61.1	2.2	58.9	63.5	69.1	2.2	66.9	72.1

TABLE 30

Percent Release in 5% Ethanol								
Time (Min)	OC			APAP				
	Mean	RSD	Mini- mum	Maxi- mum	Mean	RSD	Mini- mum	Maxi- mum
15	31.2	2.4	30.2	32.4	52.1	1.5	50.5	53.5
30	36.9	3.2	35.1	39.0	54.9	1.6	53.4	56.4
45	41.5	3.3	39.1	44.0	57.2	1.5	55.7	58.7
60	45.5	3.5	43.4	48.2	59.4	1.5	57.9	60.9
75	49.4	2.6	47.9	52.5	61.5	1.5	60.0	63.0
90	52.9	3.5	50.7	56.1	63.4	1.5	61.9	65.0
105	56.2	1.8	54.0	57.8	65.4	1.5	63.8	66.9
120	59.3	2.8	56.7	61.7	67.2	1.5	65.6	68.7

TABLE 31

Percent Release in 20% Ethanol								
Time (Min)	OC			APAP				
	Mean	RSD	Mini- mum	Maxi- mum	Mean	RSD	Mini- mum	Maxi- mum
15	28.5	4.1	26.5	30.3	51.3	2.9	48.2	53.1
30	33.6	3.3	32.3	35.7	54.1	2.3	51.3	55.7
45	38.3	2.8	35.7	39.9	56.3	2.2	53.7	58.0
60	41.8	3.6	38.1	44.1	58.3	2.1	55.6	59.9
75	45.6	3.0	43.4	48.8	60.2	2.0	57.7	61.8
90	48.7	3.3	46.1	52.0	62.0	2.0	59.4	63.6
105	51.4	3.0	49.1	53.7	63.7	1.9	61.1	65.2
120	54.3	2.7	51.3	56.7	65.4	1.9	62.9	66.8

TABLE 32

Percent Release in 40% Ethanol								
Time (Min)	OC			APAP				
	Mean	RSD	Mini- mum	Maxi- mum	Mean	RSD	Mini- mum	Maxi- mum
15	10.3	16.3	7.8	13.7	20.7	16.3	15.8	25.9
30	20.7	8.6	16.5	23.0	37.1	7.7	31.4	41.4
45	28.6	10.4	24.4	33.4	44.4	2.6	42.2	45.8
60	31.3	5.9	29.2	35.0	47.0	1.4	45.9	48.0
75	34.5	6.5	30.3	38.1	49.0	1.4	47.7	49.8
90	36.8	7.0	33.9	41.2	50.5	1.5	49.2	51.6
105	38.5	6.8	35.3	44.0	51.9	1.7	50.4	53.1
120	40.7	4.5	38.0	43.5	53.2	1.4	51.5	54.1

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Example 9

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of Oxycodone/Acetaminophen Administered Under Fed and Fasted Conditions

An open-label, randomized, three-period crossover study was conducted to evaluate the pharmacokinetics (PK), bioavailability, and safety of two tablets of a multi-layer extended-release formulation (each tablet comprising 7.5 mg oxycodone hydrochloride/325 mg acetaminophen), administered as a single dose in normal, healthy subjects under fed (high-fat or low-fat meal) and fasted conditions (i.e., 10 hr fast).

This single center, open-label, randomized, 3-period, 6-sequence crossover study in normal, healthy subjects was designed to evaluate the effect of a high-fat and low-fat meal on the PK, bioavailability, and safety of a multilayer ER tablet formulation of 7.5 mg OC/325 mg APAP (see selected example from Chart No. 1). The formulation was orally administered as 2 tablets (15 mg OC/650 mg APAP total dose) under 2 types of fed (high-fat and low-fat) and fasted conditions. Forty-eight subjects were enrolled and 31 subjects completed the study. Only subjects that completed all 3 study periods have been included in the PK evaluation.

Following a 10 hour overnight fast, subjects randomized to Treatment A consumed an entire standardized FDA high-fat breakfast (approximately 1,000±100 calories and approximately 50% from fat); those receiving Treatment B consumed an entire low-fat breakfast (approximately 800±80 calories and approximately 25% to 30% from fat). Breakfasts were consumed within 30 minutes prior to Hour 0 study drug administration. Subjects who could not consume the entire breakfast in the allotted time were dropped from the study. Subjects randomized to Treatment C were administered study drug under fasted conditions following an overnight fast of at least 10 hours. No food was allowed for the first 4 hours postdose. Blood samples were collected pre-dose (up to 60 minutes prior to dose), and at 15 min, 30 min, 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36 and 48 hours post-dose, and the resulting plasma samples were analyzed for OC and APAP using a validated liquid chromatography-tandem mass spectrometry assay with a linear range of 0.100 to 100 ng/mL for OC and 100 to 50,000 ng/mL for APAP. Pharmacokinetic parameters, as detailed above in Example 2, were determined.

Tables 33 and 34 presents PK parameters for OC under the three treatment conditions, and FIG. 19 presents plasma OC concentration-time profiles for the treatments. Mean plasma concentration profiles of OC revealed that OC was rapidly absorbed under both fed (high and low fat meal) and fasted conditions. There was a slight lag (median 0.25 hours) when the formulation was administered after a meal (high and low fat). The median of the time of observed maximum plasma concentrations (T_{max}) were 4 hours and 3 hours after administration under low fat and fasted conditions, respectively. Median T_{max} for OC under high fat conditions was significantly delayed, as compared to fasted conditions (5 hr vs. 3 hr; $P<0.05$). Average maximum plasma OC concentrations (C_{max}) were 19.94 ng/mL after a low fat breakfast, 17.90 ng/mL after a high fat breakfast, and 15.91 ng/mL under fasted conditions.

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TABLE 33

Oxycodone Pharmacokinetic Estimates (2 tablets of 7.5/325)			
Parameter	Treatment A High Fat Mean (SD) (N = 31)	Treatment B Low Fat Mean (SD) (N = 31)	Treatment C Fasted Mean (SD) (N = 31)
AUC _{0-t} (ng · h/mL)	219.41 (54.07)	219.49 (57.29)	190.70 (50.03)
AUC _{0-inf} (ng · h/mL)	221.00 (54.14)	221.38 (56.95)	192.63 (49.69)
C _{max} (ng/mL)	17.90 (4.25)	19.94 (4.66)	15.91 (3.43)
T _{max} (h) ^a	5.00 (1.00-12.00)	4.00 (1.00-5.00)	3.00 (0.75-8.00)
K _{el} (1/h)	0.1682 (0.0298)	0.1693 (0.0321)	0.1502 (0.0269)
t _{lag} (h) ^a	0.25 (0.00-1.00)	0.25 (0.00-0.75)	0.00 (0.00-0.25)
t _{1/2} (h)	4.26 (0.83)	4.26 (0.91)	4.76 (0.87)

^aMedian (minimum – maximum).

A comparison of C_{max} showed that OC concentrations were 12% and 25% higher when the formulation was given under high fat (Treatment A) and low fat (Treatment B) conditions, compared to fasted conditions (Treatment C; see Table 33). The C_{max} for Treatment A was bioequivalent to both Treatments B (84%-96%) and C (105%-120%) as the 90% CIs for the geometric ratios were contained within 80% to 125% (see Table 34). The C_{max} observed for Treatment B was not bioequivalent to Treatment C (117%-134%). AUCs were approximately 15% higher when the formulation was administered under fed conditions (high and low fat), as compared to fasted conditions (Table 33). AUC for both Treatments A and B (high fat and low fat) were bioequivalent to Treatment C (fasted; 111%-121% and 111%-120% for AUC_{0-t} and 111%-120% and 110%-120% for AUC_{0-inf}) (Table 34). The apparent plasma terminal elimination half-life (t_{1/2}) for OC was similar when the formulation was administered under fed (4 hours) and fasted conditions (5 hours).

TABLE 34

Oxycodone Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment NC Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment NB Fed (High Fat)/ Fed (Low Fat)
AUC _{0-inf} (ng · h/mL) ^a	115.41 (110.63, 120.41)	115.09 (110.38, 120.01)	100.28 (96.18, 104.55)
AUC _{0-t} (ng · h/mL) ^a	115.85 (111.00, 120.90)	115.30 (110.54, 120.27)	100.47 (96.34, 104.79)
C _{max} (ng/mL) ^a	112.11 (104.61, 120.16)	125.16 (116.88, 134.03)	89.57 (83.67, 95.90)

^aN = 31.

PK parameters for APAP are presented in Tables 35 and 36 and the plasma APAP concentration-time profiles are presented in FIG. 20. APAP was rapidly absorbed following administration under fed (high and low fat meals) and fasted conditions. There was a slight lag when the formulation was administered after a low fat breakfast (median lag time [t_{lag}] 0.25 hours). There was no lag in the absorption of APAP when administered following a high fast breakfast or after fasting. The time to C_{max} was significantly (P<0.05) longer when administered after a meal (high and low fat; median T_{max}=2 hours) than when administered under fasted conditions (me-

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dian T_{max}=0.5 hour). Average C_{max} values for APAP were lower after a high (3,775 ng/mL) and low fat (3,863 ng/mL) meal than when administered under fasted conditions (5,175 ng/mL). Geometric mean ratios for C_{max} following Treatments A and B were 24% to 23% lower than for Treatment C (Table 36). The 90% CIs for C_{max} following Treatment A (70%-82%) and Treatment B (72%-83%) with reference to fasted state were outside the bioequivalent range of 80%-125%. The AUCs for APAP were almost identical when the formulation was administered under high fat, low fat, or fasted conditions. (Comparison of geometric mean ratios of AUC_{0-t} and AUC_{0-inf} for Treatments A (90% CI 97%-103% and 96%-102%) and B (90% CI 96%-101% and 94% to 100%) with those for Treatment C showed that treatments were bioequivalent. The t_{1/2} for APAP after the formulation was administered after a high or low fat meal (5 hours) was slightly shorter than when administered under fasted conditions (7 hours).

TABLE 35

APAP Pharmacokinetic Estimates (2 tablets of 7.5/325)			
Parameter	Treatment A Fed (High Fat) Mean (SD) (N = 31)	Treatment B Fed (Low Fat) Mean (SD) (N = 31)	Treatment C Fasted Mean (SD) (N = 31)
AUC _{0-t} (ng · h/mL)	29617.96 (7765.99)	29346.82 (7869.75)	29763.19 (7592.89)
AUC _{0-inf} (ng · h/mL)	31457.06 (7973.16) ^a	30550.48 (8051.47)	31807.70 (7923.30) ^a
C _{max} (ng/mL)	3774.52 (949.84)	3862.90 (978.08)	5175.48 (1731.31)
T _{max} (h) ^b	2.00 (0.50-5.00)	2.00 (0.50-5.00)	0.53 (0.23-5.00)
K _{el} (1/h)	0.1564 (0.0363) ^a	0.1593 (0.0408)	0.1146 (0.0360) ^a
t _{lag} (h) ^b	0.00 (0.00-1.00)	0.25 (0.00-0.50)	0.00 (0.00-0.25)
t _{1/2} (h)	4.66 (1.08) ^a	4.71 (1.60)	6.63 (1.99) ^a

^aN = 29^bMedian (minimum – maximum).

TABLE 36

APAP Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment A/C Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment A/B Fed (High Fat)/ Fed (Low Fat)
AUC _{0-inf} (ng · h/mL) ^a	98.60 (95.75, 101.54)	96.56 (93.80, 99.39)	102.12 (99.20, 105.11)
AUC _{0-t} (ng · h/mL) ^b	99.88 (97.31, 102.52)	98.79 (96.27, 101.37)	101.10 (98.54, 103.74)
C _{max} (ng/mL) ^b	76.00 (70.49, 81.94)	77.18 (71.65, 83.13)	98.48 (91.45, 106.05)

^aN = 27^bN = 31

In summary, total exposure (AUC) for OC was slightly increased (by about 15%) when the formulation was administered with food (after high- or low-fat meal); however, AUCs for OC were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted and high fat vs. low fat). Peak exposure (C_{max}) for OC was 12% and 25% higher under high fat and low-fat conditions, respectively, compared to fasted conditions. The C_{max} for OC after a high-fat meal was bioequivalent to fasted conditions, as well as to low fat conditions, whereas the C_{max} under low fat conditions was not

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equivalent to those under fasted conditions. The AUCs for APAP were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted, and high fat vs. low fat). The peak exposure (C_{max}) for APAP was decreased by about 24% in fed (high- and low-fat) states as compared to the fasted state.

Example 10

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Oxycodone/325 mg Acetaminophen—Single Dose

An open-label, randomized, 3-period crossover study was performed to evaluate the single dose pharmacokinetic (PK) parameters, bioavailability, and safety of an extended-release formulation containing 7.5 mg OC/325 mg APAP (see selected example from Chart No. 1) in healthy subjects under fasted conditions. The PK and bioavailability of the extended-release formulation administered as 1 or 2 tablets were compared to the commercially-available immediate release tablet (immediate release 7.5 mg OC/325 mg APAP) administered as 1 or 2 tablets every 6 hours for 2 doses. This study was conducted in 48 male and female subjects, with equal gender distribution.

Pharmacokinetic parameter estimates for OC are presented in Table 37, and OC plasma concentration-time profiles are presented in FIG. 21. There was no lag in absorption of OC for the 1 and 2 tablet dosing configurations of the extended release formulation and the commercially-available immediate release tablet under fasted conditions. Plasma concentrations of OC rose rapidly after administration of the extended release formulation in a similar fashion to the commercially-available immediate release tablet, and peak plasma levels of OC were observed (T_{max}) at 4 and 3 hours for the 1 or 2 tablet dosing configuration of the extended release formulation compared with 7 hours after the initial dose of 1 tablet of the commercially-available immediate release tablet (1 hour after the second dose) and 0.75 hours after the initial dose of 2 tablets of the commercially-available immediate release tablet. Mean plasma concentrations of OC from the extended release formulation were detectable through 36 hours in most subjects following all treatments and $t_{1/2}$ was about 4 to 5 hours across all treatments. The extent of exposure (AUC_{0-t} and AUC_{0-inf}) for the 2 tablet dosing configuration of the extended release formulation increased proportionally with dose compared with the 1-tablet dosing configuration of the extended release formulation.

TABLE 37

Oxycodone Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
AUC_{0-t} (ng · h/mL)	87.43 (24.59)	185.98 (47.64)	191.15 (53.43)	401.23 (110.56)
AUC_{0-inf} (ng · h/mL)	89.85 (24.73) ^b	187.71 (47.58)	193.10 (53.22)	403.04 (110.45)
C_{max} (ng/mL)	8.41 (2.06)	16.39 (4.31)	20.82 (5.98)	41.24 (12.12)

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TABLE 37-continued

Oxycodone Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
T_{max} (h) ^a	4.00 (0.75-5.92)	3.00 (0.75-6.50)	7.38 (0.50-10.00)	0.75 (0.50-12.00)
t_{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.52)	0.00 (0.00-0.25)	0.00 (0.00-0.25)
$t_{1/2}$ (h)	4.50 (0.78) ^b	4.87 (0.93)	4.08 (0.89)	4.34 (1.02)
K_{el} (h ⁻¹)	0.1590 (0.0307) ^b	0.1473 (0.0274)	0.1770 (0.0352)	0.1688 (0.0415)

^aMedian (minimum – maximum).^bN = 32

No dose-dumping was observed in any subject receiving the ER formulation. The interindividual variability (CV %) for C_{max} of OC after administration of 1 or 2 tablets of the ER formulation was comparable to 1 tablet of the commercially-available immediate release tablet and less than 29% for all 3 treatments. Similarly the interindividual variability (CV %) for AUC of OC was 28% or less for 1 and 2 tablets of the ER formulation and 1 tablet of the commercially-available immediate release tablet.

Table 38 presents APAP PK parameter estimates and FIG. 22 presents APAP plasma concentration-time profiles. The appearance of plasma concentrations of APAP for all dose configurations of the extended release formulation and the commercially-available immediate release tablet showed no lag. Plasma concentrations of APAP rose rapidly after administration of the extended release formulation, similar to that observed with the commercially-available immediate release tablet. Peak plasma levels of APAP following administration of the 1 tablet and 2 tablet dosing configurations of the extended release formulation were observed (median T_{max}) at 0.75 hours after dosing compared with 0.5 hours after the first dose of the commercially-available immediate release tablet (1 and 2 tablets). Mean plasma concentrations of APAP were detectable through 36 hours following all treatments and the mean $t_{1/2}$ was approximately 4 to 7 hours across treatment groups. The extent of exposure (AUC) to APAP following dosing with 1 and 2 tablets of the extended release formulation increased proportionally with dose.

TABLE 38

APAP Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
AUC_{0-t} (ng · h/mL)	15871 (4841)	32665 (10894)	33040 (9589)	69837 (22945)
AUC_{0-inf} (ng · h/mL)	16995 (5073)	34836 (11067) ^b	34236 (10126) ^b	71949 (24234) ^c
C_{max} (ng/mL)	2632 (918)	5230 (2086)	4878 (1545)	10741 (4123)

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TABLE 38-continued

APAP Pharmacokinetic Estimates (7.5/325)				
	Treatment A	Treatment B	Treatment C	Treatment D
	ER	ER	Commercially-	Commercially-
	Formulation	Formulation	available	available
	(1 tablet)	(2 tablets)	immediate	immediate
Parameter	Mean (SD)	Mean (SD)	release tablet	release tablet
	(N = 33)	(N = 33)	(1 tablet twice)	(2 tablets twice)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	(N = 33)	(N = 33)	(N = 33)	(N = 27)
T_{max} (h) ^a	0.75	0.75	0.50	0.50
	(0.25-2.02)	(0.25-4.00)	(0.25-9.00)	(0.25-12.00)
t_{lag} (h) ^a	0.00	0.00	0.00	0.00
	(0.00-0.50)	(0.00-0.25)	(0.00-0.00)	(0.00-0.00)
$t_{1/2}$ (h)	5.33	6.88	4.41	5.76
	(1.53)	(2.15) ^b	(1.16) ^b	(1.47) ^c
K_{el} (h ⁻¹)	0.1421	0.1103	0.1669	0.1291
	(0.0479)	(0.0337) ^b	(0.0411) ^b	(0.0368) ^c

^aMedian (minimum – maximum).^bN = 32^cN = 25

No dose-dumping was observed in any subject receiving the ER formulation. The interindividual variability (CV %) for C_{max} of APAP was slightly more after administration of 1 and 2 tablets of the ER formulation (35% and 40%, respectively) than for 1 tablet of the commercially-available immediate release tablet (32%). The interindividual variability (CV %) for AUC of APAP was less than 33% for all 3 treatments.

Both OC and APAP were rapidly absorbed under all conditions with no lag in plasma concentrations. Both OC and APAP levels were sufficiently high within 1 hour after administration of the extended release formulation. Peak exposure to OC was 18% to 21% lower for the ER formulation than for the commercially-available immediate release tablet (1 tablet Q6h). OC levels were sustained over the proposed 12 h dosing interval. By 12 hours after dosing with the extended release formulation, APAP plasma levels were less than 20% of C_{max} . Total exposure to both OC and APAP from the extended release formulation was equivalent to that of 1 tablet of the commercially-available immediate release tablet.

To further analyze the absorption of OC and APAP from the ER formulation, the plasma concentrations of OC and APAP following administration of 1 tablet of the ER formulation, 2 tablets of the ER formulation, and the commercially-available immediate release tablet were deconvolved using WinNonlin 5.2 (Pharsight). Deconvolution evaluates in vivo drug release and delivery based on data for a known drug input. Depending upon the type of reference input information available, the drug transport evaluated will be either a simple in vivo drug release (e.g., gastro-intestinal release) or a composite form, typically consisting of an in vivo release followed by a drug delivery to the general systemic circulation. It can estimate the cumulative amount and fraction absorbed over time for the subjects, given PK profile data and dose. For a pure immediate release (IR) or an extended release (ER) formulation the cumulative absorption plot shows a monoexponential curve whereas for a bilayer formulation (IR+ER) a biexponential (rapid phase followed by slower phase) absorption curve will be observed. FIG. 23 and FIG. 24 present the deconvolution plots for OC and APAP, respectively. For each, there is an early rapid phase of absorption that is followed by a later slower phase of absorption from the ER formulation.

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Example 11

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Oxycodone/325 mg Acetaminophen—Multiple Doses

An open-label, randomized, 3-period crossover study was performed to evaluate the steady-state PK, bioavailability, and safety of the extended release formulation containing 7.5 mg OC/325 mg APAP in healthy subjects (see selected example from Chart No. 1). The PK and bioavailability of the ER formulation administered as 1 or 2 tablets every 12 hours for 4.5 days (9 doses) was compared to the commercially-available immediate release tablet (immediate release 7.5 mg OC/325 mg APAP) administered as 1 tablet every 6 hours for 4.5 days (18 doses) under fasted conditions (10 hours for the first dose on Days 1 and 5; at least 1 hour for all other doses). This study was conducted in 48 male and female subjects, with equal gender distribution.

The PK behavior of OC on Study Day 1 (see Table 39) was similar to that observed in the single dose study (see Example 10). There was no lag (median t_{lag} 0 hours) in the absorption of OC following administration of the ER formulation (1 or 2 tablets) and the commercially-available immediate release tablet, and no dose-dumping was observed for any subject. Peak plasma levels were observed at 3 hours after administration of 1 and 2 tablets of the ER formulation and at 1 hour after the second dose of the commercially-available immediate release tablet (FIG. 25). On Day 1, interindividual variability (% CV) in the C_{max} for OC was slightly higher for 1 tablet (29%) than for 2 tablets (23%) of the ER formulation or the commercially-available immediate release tablet (up to 22%). The variability in the AUC_{0-12h} for OC was comparable between all 3 treatments (21% to 23%). Minimum (trough) plasma concentrations (Cmin) of OC achieved steady-state levels by Day 4 for 1 tablet of the ER formulation and the commercially-available immediate release tablet and by Day 3 for 2 tablets of the ER formulation. Trough levels of OC on Days 2 through 5 for 2 tablets of the ER formulation were comparable to those observed for the commercially-available immediate release tablet.

TABLE 39

Oxycodone Pharmacokinetic Estimates - Day 1			
	Treatment A	Treatment B	Treatment C
	ER Formulation	ER Formulation	Commercially-
	(1 Tablet Q12 h)	(2 Tablets Q12 h)	available
	Mean (SD)	Mean (SD)	immediate
Parameter	(N = 33)	(N = 33)	release tablet
	Mean (SD)	Mean (SD)	(1 Tablet Q6 h)
	(N = 33)	(N = 33)	Mean (SD)
	(N = 33)	(N = 33)	(N = 33)
AUC_{0-12h}	66.93	135.89	141.73
(ng · h/mL)	(15.14)	(30.81)	(29.78)
C_{max}	8.34	17.05	21.93
(ng/mL)	(2.37)	(3.97)	(4.80)
T_{max} (h) ^a	3.00	3.00	7.00
	(0.75-7.00)	(0.50-5.92)	(0.50-8.00)
t_{lag} (h) ^a	0.00	0.00	0.00
	(0.00-0.50)	(0.00-0.32)	(0.00-0.25)

^aMedian (minimum – maximum).

On Day 5 (see Table 40), steady state was achieved and the median T_{max}^{ss} was observed at 2 hours following 1 tablet or 2 tablets of the ER formulation and at 30 min following the second daily dose of the commercially-available immediate release tablet. Maximum observed plasma concentrations at

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steady-state (C_{max}^{ss}) for OC for the 1 and 2 tablet dosing configurations of the ER formulation were not equivalent to the commercially-available immediate release tablet. On Day 5, interindividual variability (% CV) in C_{max}^{ss} and AUC_{0-12h}^{ss} for OC was comparable between all 3 treatments (up to 29%). The degree of fluctuation (DFL) in and the swing of plasma concentrations for the ER formulation over the last 12 hour dosing interval on Day 5 were 15% to 22% less than that observed for the commercially-available immediate release tablet.

TABLE 40

Oxycodone Pharmacokinetic Estimates - Day 5			
Parameter	Treatment A ER Formulation (1 Tablet Q12 h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12 h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6 h) Mean (SD) (N = 33)
AUC_{0-12h}^{ss} (ng · h/mL)	102.36 (29.30)	208.59 (59.28)	208.93 (57.30)
C_{av}^{ss} (ng/mL)	8.53 (2.44)	17.38 (4.94)	17.41 (4.78)
C_{max}^{ss} (ng/mL)	12.67 (3.48)	25.67 (7.49)	30.50 (8.91)
C_{min}^{ss} (ng/mL)	4.06 (1.40)	8.98 (3.52)	8.78 (3.17)
DFL (%)	101.72 (14.14)	97.17 (18.80)	126.83 (27.93)
Swing	2.23 (0.64)	2.03 (0.70)	2.67 (0.92)
T_{max}^{ss} (h) ^a	2.00 (0.50-10.00)	2.00 (0.50-7.00)	6.50 (0.50-8.02)
$t_{1/2}$ (h) ^c	5.46 (1.24)	6.11 (1.46)	5.47 (1.70) ^b
K_{el} (1/h) ^c	0.1326 (0.0269)	0.1199 (0.0291)	0.1387 (0.0418) ^b

^aMedian (minimum – maximum).^bN = 32^cDays 5 to 7.

The PK behavior of APAP on Study Day 1 (see Table 41) was similar to that observed in the single dose study (see Example 10). Acetaminophen was rapidly absorbed following a single dose of 1 or 2 tablets of the ER formulation and in a similar fashion to the commercially-available immediate release tablet. (See FIG. 26). There was no lag in plasma concentrations following any of the 3 dosing regimens (median t_{lag} 0 hours), and no dose-dumping was observed for any subject. Peak APAP plasma concentrations were observed 30 to 45 minutes after administration of 1 or 2 tablets of the ER formulation and at 30 minutes after the first dose of the commercially-available immediate release tablet on Day 1. The C_{max} for APAP occurred following the first 325 mg dose of the commercially-available immediate release tablet, rather than after the second dose. Dose proportionality for C_{max} and AUC_{0-12h} was observed over the range of 325 mg to 650 mg APAP after a single administration of 1 or 2 tablets of the ER formulation. The C_{min} of APAP achieved steady-state levels by Day 4 for 1 tablet and by Day 2 for 2 tablets of the ER formulation and for the commercially-available immediate release tablet. Trough levels of APAP on Days 2 through 5 for 2 tablets of the ER formulation were comparable to those observed for the commercially-available immediate release tablet. On Day 1, interindividual variability (% CV) in C_{max} and AUC_{0-12h} for APAP was comparable between all 3 treatments (31% or less).

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TABLE 41

APAP Pharmacokinetic Estimates - Day 1			
Parameter	Treatment A ER Formulation (1 Tablet Q12 h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12 h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6 h) Mean (SD) (N = 33)
AUC_{0-12h} (ng · h/mL)	12192 (3331)	24141 (6436)	24884 (6656)
C_{max} (ng/mL)	2631 (815)	5245 (1473)	5146 (1553)
T_{max} (h) ^a	0.55 (0.25-3.00)	0.75 (0.25-2.00)	0.50 (0.25-8.00)
t_{lag} (h) ^a	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.00 (0.00-0.00)

^aMedian (minimum – maximum).

On Day 5 of the study, median T_{max}^{ss} for APAP was observed at 30 minutes following 1 or 2 tablets of the ER formulation and at 30 minutes following the first daily dose of the commercially-available immediate release tablet (see Table 42). Acetaminophen concentrations following administration of 325 mg or 650 mg APAP (1 or 2 tablets) Q12h were proportional to dose. The DFL in and swing of plasma APAP levels for the ER formulation were equivalent to the commercially-available immediate release tablet. On Day 5, interindividual variability (% CV) in C_{max}^{ss} for APAP was slightly higher following administration of 2 tablets of the ER formulation (33%) than the % CV seen for 1 tablet of the ER formulation and the commercially-available immediate release tablet (~27%). Interindividual variability in AUC_{0-12h}^{ss} for APAP was comparable between all 3 treatments (up to 27%).

TABLE 42

APAP Pharmacokinetic Estimates - Day 5			
Parameter	Treatment A ER Formulation (1 Tablet Q12 h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12 h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6 h) Mean (SD) (N = 33)
AUC_{0-12h}^{ss} (ng · h/mL)	15307 (4092)	28512 (7714)	28719 (7023)
C_{av}^{ss} (ng/mL)	1276 (341)	2376 (643)	2393 (585)
C_{max}^{ss} (ng/mL)	3117 (840)	5872 (1932)	5968 (1639)
C_{min}^{ss} (ng/mL)	474.67 (163)	870.42 (336)	922.58 (321)
DFL (%)	212.08 (52.29)	218.06 (81.14)	213.79 (50.53)
Swing	5.95 (2.04)	6.63 (3.61)	5.94 (2.24)
T_{max}^{ss} (h) ^a	0.50 (0.25-3.00)	0.50 (0.25-3.02)	0.50 (0.25-8.02)
$t_{1/2}$ (h) ^c	5.60 (1.35) ^b	7.47 (2.89)	5.74 (2.98) ^b
K_{el} (1/h) ^c	0.1308 (0.0317) ^b	0.1026 (0.0292)	0.1416 (0.0515) ^b

^aMedian (minimum – maximum).^bN = 31^cDays 5 to 7.

Both OC and APAP were rapidly absorbed under all conditions with no lag in plasma concentrations. Both OC and APAP levels were sufficiently high within 1 hour after admin-

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istration of the ER formulation as a single dose and at steady-state. OC levels were sustained over the proposed 12h dosing interval. Plasma APAP concentrations decreased to below 1,000 ng/mL between doses of the ER formulation, thus minimizing the chances of its accumulation and the possibility of hepatotoxicity. Total exposure to both OC and APAP from the ER formulation was equivalent to that of the commercially-available immediate release tablet.

Example 12

Clinical Evaluation of the Safety and Analgesic Efficacy of an Extended Release Formulation of Oxycodone and Acetaminophen for Acute Pain

Pain relief for acute post-surgical pain requires immediate-release (IR) compounds acting within 1 hour of administration. These IR compounds, however, have a short half-life and require frequent administration; this is inconvenient to patients and leads to poor compliance. Such patients may benefit from an extended-release (ER) oral formulation of oxycodone hydrochloride (OC) and acetaminophen (APAP) that is designed to (1) provide the immediate-release of each drug to attain rapid therapeutic levels (within 1 hour of dosing) and (2) provide continuous release of each drug to maintain the plasma levels of each drug within therapeutic windows for sustained analgesia (up to 12 hours). Furthermore, combining analgesics with distinct mechanisms of action provides maximum efficacy while reducing the toxicity of each agent, as the amount of OC and APAP can remain within the lower, safer end of their therapeutic windows. This ER formulation may provide the advantages of both immediate and prolonged pain relief from two analgesic compounds, potentially offering greater convenience to patients and greater dosing compliance. Accordingly, a study may be conducted to demonstrate the efficacy of repeated doses of 15 mg OC/650 mg APAP versus placebo, and to determine the safety and tolerability of multiple oral doses of the OC/APAP formulation administered to subjects with acute postoperative, moderate to severe pain.

The study will be conducted in the following phases: 1) pre-treatment phase consisting of a) screening, b) surgery, and c) recovery/qualification periods; 2) double-blind phase consisting of a single dose period followed by a multiple-dose period which begins with the request of the 2nd dose of study medication, and; 3) a voluntary open-label extension phase.

The single dose period of the double-blind phase will evaluate the onset and duration of analgesia of a single dose of 15 mg OC/650 mg APAP (as two 7.5/325 tablets) versus placebo. The time from the initial dose of study medication to the onset of perceptible pain relief and to the onset of meaningful pain relief will be measured. The subject will provide additional pain assessments (e.g., pain intensity will be measured using the 11 point NPRS scale at regular intervals).

The multiple dose period of the double-blind phase will evaluate the analgesic effects of multiple doses of 15 mg OC/650 mg APAP versus placebo with subjects dosed regularly every 12 hours for 48 hours. The multiple dose period will begin upon administration of the second dose after the subject's request for additional pain relief. Pain relief and intensity will be among the data measured in this arm of the study.

After completion of study evaluations 48 hours after the 2nd dose of study medication, subjects will be encouraged to enter the open-label extension phase of the study. During this

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time they will be provided with doses of 15 mg OC/650 mg APAP to be taken Q12h until no longer needed, for up to 14 days. The open-label extension phase (starting 48 hours after the second dose) will evaluate the safety profile as determined by adverse events (AE) and evaluate subject satisfaction with analgesic effects.

Example 13

Clinical Evaluation of the Safety and Efficacy of an Extended Release Formulation of Oxycodone and Acetaminophen for Chronic Pain

An open label safety study of doses of 15 mg OC/650 mg APAP administered at 12 hour intervals for up to 35 days in a patient population having pain associated with osteoarthritis (OA) of the knee or hip or chronic low back pain (CLBP) may be conducted. The primary objective of the study is to determine the safety and tolerability of doses of 15 mg OC/650 mg APAP for up to 35 days of use. Secondary objectives such as pain relief and changes in pain intensity will also be assessed.

Subjects enrolled in the study will be treated with 2 tablets of 7.5 mg OC/325 mg APAP every 12 hours (Q12h) for between 10 days and 35 days. Subjects will initially take 1 tablet of 7.5 mg OC/325 mg APAP under clinic supervision. Subjects will be observed for opioid tolerability symptoms. Subjects who experience opioid tolerability symptoms, or moderate to severe AEs, will be discontinued from the study. Subjects who do not experience opioid tolerability symptoms, or moderate to severe AEs, will be given a second tablet of 7.5 mg OC/325 mg APAP under clinic supervision. If subjects still do not experience opioid tolerability symptoms, or moderate to severe AEs, they will be sent home with supplies for dosing with 2 tablets of 7.5 mg OC/325 mg APAP Q12h for one week. If subjects do experience opioid tolerability symptoms, or moderate to severe AEs, they will be sent home with supplies for dosing with 1 tablet of 7.5 mg OC/325 mg APAP Q12h for one week.

Subjects that continue in the study beyond one week will continue to take 2 tablets Q12h for up to a total of 35 days, during which they will return to the clinic for subsequent assessments of safety and efficacy. After the Day 36 visit, subjects will be instructed to return to pre-study medication. Subjects whose pain subsides prior to the Day 36 visit, or who discontinue for other reasons will be instructed to return remaining study medication.

Example 14

Partial Areas Under the Curve for Oxycodone and Acetaminophen

Partial AUCs were calculated for a bilayer extended release tablet disclosed herein containing acetaminophen and oxycodone, and an immediate release acetaminophen and oxycodone tablet. Specifically, Partial AUCs were calculated for the acetaminophen and oxycodone tablets of (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10. These results are summarized in Tables 43-46.

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TABLE 43

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen				
Study	AUC _{0-1.7h} (ng · h/mL)	AUC _{1.7-48h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)	
Treatment B (Ex. 10)	6029	28435	32644	
Treatment C (Ex. 9)	5854	25539	29741	

TABLE 44

Additional Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen					
Study	AUC _{0-12h} (ng · h/mL)	AUC _{1-12h} (ng · h/mL)	AUC _{12-36h} (ng · h/mL)	AUC _{8-12h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment B (Ex. 10)	25912	22615	7978	4401	32644
Treatment C (Ex. 9)	24102	20875	6854	3910	29741

TABLE 45

Percent of AUC _{0-t} for Acetaminophen				
Study	AUC _{0-12h} (dosing interval)	AUC _{1-12h} (T _{max} to end of dosing interval)	AUC _{12-36h} (end of dosing interval to last concentration)	AUC _{8-12h}
Treatment B (Ex. 10)	79%	69%	24%	13%
Treatment C (Ex. 9)	81%	70%	23%	13%

TABLE 46

Mean(SD) Parameter Estimates for Partial AUCs for Oxycodone			
Study	AUC _{0-2.8h} (ng · h/mL)	AUC _{2.8-48h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment B (Ex. 10)	28.75	158.49	185.93
Treatment C (Ex. 9)	27.89	164.27	190.66

The bioequivalence determinations between two tablets of a pharmaceutical composition described herein, each containing 7.5 mg oxycodone and 325 mg acetaminophen and an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen can be found in Tables 47 and 48.

TABLE 47

Bioequivalence Determination for Acetaminophen			
Parameter	LSM Ratio	90% CI	
Ln(AUC _{0-1.7h})	101.97	82.90	125.43
Ln(AUC _{1.7-48h})	91.15	80.58	103.11
Ln(AUC _{0-t})	93.14	82.40	105.28

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TABLE 48

Bioequivalence Determination for Oxycodone			
Parameter	LSM Ratio	90% CI	
Ln(AUC _{0-2.8h})	99.04	87.83	111.68
Ln(AUC _{2.8-48h})	103.21	92.57	115.06
Ln(AUC _{0-t})	102.19	92.34	113.09

The results demonstrate that the plasma concentrations of both oxycodone and acetaminophen rose rapidly with no lag time for a pharmaceutical composition of the present invention and an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen. See FIGS. 29(a) and (b). Further, 30 minutes after administration of a dose of a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen), oxycodone levels were within the therapeutic range (>5 ng/mL). Thus, an analgesic effect will be seen in opioid naïve patients. In addition, a pharmaceutical composition of the present invention was able to maintain oxycodone levels above 5 ng/mL for up to 12 hours after dosing, suggesting that the analgesic effect may extend to the next dosing cycle.

Concentrations of acetaminophen resulting from a dose of a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen), decreased to less than 900 ng/mL (>17% of C_{max}) by 12 hours after administration. This decreased concentration of acetaminophen at the end of the dosing cycle allows for sufficient acetaminophen or "APAP time off" between doses.

Oxycodone and acetaminophen levels from a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen) declined at a similar rate to an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen, with a terminal elimination half-life of approximately 4 to 5 hours.

Example 15

Partial Areas Under the Curve for Oxycodone and Acetaminophen Administered with Food

Partial AUCs were calculated for a bilayer extended release tablet disclosed herein containing acetaminophen and oxycodone, and an immediate release acetaminophen and oxycodone tablet. Specifically, Partial AUCs were calculated for the acetaminophen and oxycodone tablets of 1) Treatment A of Example 4, (2) Treatment A of Example 6 (one tablet), and (3) Treatment C of Example 4. These results are summarized in Tables 49-50.

TABLE 49

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen			
Study	AUC _{0-3.2h} (ng · h/mL)	AUC _{3.2-48h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment A (Ex. 4)	8042	23810	30245
Treatment A (Ex. 6) (one tablet)	9145	23319	31478

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TABLE 50

Mean (SD) Parameter Estimates for Partial AUCs for Oxycodone.			
Study	AUC _{0-4.3h} (ng · h/mL)	AUC _{4.3-48h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment A (Ex. 4)	48.62 (15.99)	152.57 (49.86)	199.43 (59.47)
Treatment A (Ex. 6) (one tablet)	53.29 (17.12)	167.50 (51.83)	219.20 (55.99)

The bioequivalence determinations between the pharmaceutical composition described herein, containing 15 mg oxycodone and 650 mg acetaminophen and an immediate release product comprising 15 mg oxycodone and 650 mg acetaminophen can be found in Tables 51 and 52.

TABLE 51

Bioequivalence Determination for Acetaminophen			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-3.2h})	114.46	96.21	136.16
Ln(AUC _{3.2-48h})	94.62	83.31	107.47
Ln(AUC _{0-t})	101.32	90.00	114.07

TABLE 52

Bioequivalence Determination for Oxycodone			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-4.3h})	109.87	94.98	127.08
Ln(AUC _{4.3-48h})	109.75	94.48	127.48
Ln(AUC _{0-t})	110.53	97.39	125.44

Exposure to oxycodone and acetaminophen was comparable between Treatment A of Example 4 and Treatment A of Example 6 (one tablet). Thus, these results indicate that the release of oxycodone and acetaminophen is consistent across studies. Plasma concentration-time profiles are presented in FIGS. 30A and 30B.

The initial exposure to oxycodone (AUC_{0-4.3h}) was slightly outside the bioequivalence parameters established by the FDA (upper 90% CI 127%). The initial exposure to acetaminophen (AUC_{0-3.2h}) was outside of the FDA's bioequivalence parameters (upper 90% CI 136%).

The extended (sustained) exposure to oxycodone (AUC_{4.3-48h}) was slightly outside the FDA's limit for bioequivalence (upper 90% CI 127%). However, the extended exposure to acetaminophen (AUC_{3.2-48h}) and total exposure (AUC_{0-t}) for both oxycodone and acetaminophen was equivalent between studies.

Example 16

Pharmacokinetic Study Involving Hydrocodone and Acetaminophen

A four-way crossover pharmacokinetic study was conducted. In a first trial (Treatment A), thirty-five subjects in a fasted state were administered a single, two-tablet dose of hydrocodone/acetaminophen, each tablet containing 7.5 mg hydrocodone, 325 mg acetaminophen, and having slow

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release properties as compared to an immediate release formulation. (See selected examples from Chart Nos. 1 and 3). In a second trial (Treatment B), thirty-five subjects in a fasted state were administered a single, two-tablet dose of hydrocodone/acetaminophen, each tablet containing 7.5 mg hydrocodone, 325 mg acetaminophen, and having medium release properties as compared to an immediate release formulation. (See selected examples from Chart Nos. 1 and 3). In a third trial (Treatment C), thirty-five subjects in a fed state were administered a single, two-tablet medium-release dose of hydrocodone/acetaminophen, each tablet containing 7.5 mg hydrocodone, 325 mg acetaminophen, and having medium release properties as compared to an immediate release formulation. (See selected examples from Chart Nos. 1 and 3). In a fourth trial (Treatment D), thirty-five subjects were administered a single, two-tablet dose of an immediate release tablet containing 7.5 mg hydrocodone and 325 mg acetaminophen.

The pharmacokinetic profiles from time 0 to 36 hours for hydrocodone and acetaminophen in each of these trials are shown in FIGS. 31 and 32, respectively. The pharmacokinetic profiles from time 0 to 12 hours for hydrocodone and acetaminophen in each of these trials are shown in FIGS. 33 and 34, respectively. The pharmacokinetic parameters of hydrocodone and acetaminophen are summarized in Tables 53 and 54, respectively. The simulated pharmacokinetic profiles from time 0 to 144 hours for hydrocodone and acetaminophen in each of these trials are shown in FIGS. 35 and 36, respectively.

TABLE 53

Pharmacokinetic parameters for hydrocodone				
Parameter	Treatment A, Mean (SD) (N = 35)	Treatment B, Mean (SD) (N = 35)	Treatment C, Mean (SD) (N = 35)	Treatment D, Mean (SD) (N = 35)
AUC _{0-t} (ng · h/mL)	254.12 (71.48)	243.88 (67.86)	265.08 (73.62)	261.60 (72.55)
AUC _{0-inf} (ng · h/mL)	264.47 (72.66)	251.04 (69.72)	268.73 (75.25)	264.79 (73.55)
C _{max} (ng/mL)	18.62 (5.38)	18.93 (5.58)	19.73 (4.06)	22.84 (6.51)
T _{max} (h) ^a	4.05 (2.00-7.00)	4.00 (1.00-7.00)	5.92 (2.00-12.08)	8.00 (0.67-10.02)
t _{lag} (h) ^a	0.17 (0.00-0.37)	0.17 (0.00-0.48)	0.17 (0.00-0.67)	0.17 (0.00-0.33)
t _{1/2} (h)	7.14 (2.55)	6.70 (1.56)	4.91 (0.59)	4.87 (0.57)
K _{el} (h ⁻¹)	0.1087 (0.0351)	0.1087 (0.0238)	0.1431 (0.0174)	0.1442 (0.0171)

^aMedian (minimum-maximum).

TABLE 54

Pharmacokinetic parameters for acetaminophen				
Parameter	Treatment A, Mean (SD) (N = 35)	Treatment B, Mean (SD) (N = 35)	Treatment C, Mean (SD) (N = 35)	Treatment D Mean (SD) (N = 35)
AUC _{0-t} (ng · h/mL)	30578 (9205)	28939 (8364)	29900 (8544)	30771 (9518)
AUC _{0-inf} (ng · h/mL)	33417 (9306)	31073 (8688)	31512 (8943)	31833 (9831)
C _{max} (ng/mL)	5030 (1678)	4950 (1586)	3343 (847)	4755 (1673)
T _{max} (h) ^a	0.67 (0.33-2.00)	0.67 (0.22-1.03)	2.00 (0.33-5.92)	0.67 (0.33-7.00)
t _{lag} (h) ^a	0.00 (0.00-0.33)	0.00 (0.00-0.17)	0.17 (0.00-0.50)	0.00 (0.00-0.33)
t _{1/2} (h)	8.05 (3.33)	6.57 (2.11)	5.10 (2.24)	4.36 (1.32)
K _{el} (h ⁻¹)	0.1030 (0.0478)	0.1196 (0.0504)	0.1529 (0.0498)	0.1718 (0.0509)

^aMedian (minimum-maximum).

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These results indicate that the subjects exhibited an initial rapid rise in hydrocodone concentrations to provide early onset of action with the concentrations falling slowly over a period of twelve hours. The median T_{lag} was unaffected by the formulations in comparison to an immediate release tablet containing 7.5 mg hydrocodone and 325 mg acetaminophen. Subjects also exhibited an initial rapid rise in acetaminophen concentrations to provide the desired early onset of action with the concentrations reaching levels that were lower than an immediate release tablet containing 7.5 mg hydrocodone and 325 mg acetaminophen at around twelve hours. Accordingly, the pharmaceutical compositions administered in Treatments A-C exhibited the desired APAP "time-off" feature in their pharmacokinetic profiles.

Administration of the pharmaceutical formulations with food had no effect on C_{max} and AUC of hydrocodone, although the T_{max} was delayed by two hours. T_{lag} was unaffected. The C_{max} of APAP decreased by about 31% when administered with food, but there was no change in AUC. T_{max} of APAP was delayed by a little more than one hour. No dose dumping was observed from any of the formulations.

The pharmacokinetic profiles of both the pharmaceutical formulations having slow and medium release properties as compared to an immediate release formulation satisfy the desired pharmacokinetic parameters for both hydrocodone and acetaminophen. The observed C_{max} and AUC values were suitable for hydrocodone/acetaminophen formulations containing an immediate release and extended release portion.

Example 17

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of Hydrocodone/Acetaminophen Administered Under Fed and Fasted Conditions

An open-label, randomized, three-period crossover study was conducted to evaluate the pharmacokinetics (PK), bioavailability, and safety of two tablets of a multi-layer extended-release formulation (7.5 mg hydrocodone bitartrate (HB)/325 mg acetaminophen (APAP)), administered as a single dose in normal, healthy subjects under fed (high-fat or low-fat meal) and fasted conditions (i.e., 10 hr fast).

This single center, open-label, randomized, 3-period, 6-sequence crossover study in normal, healthy subjects was designed to evaluate the effect of a high-fat and low-fat meal on the PK, bioavailability, and safety of a multilayer ER tablet formulation of 7.5 mg HB/325 mg APAP (see selected example from Chart Nos. 1 and 3). The formulation was orally administered as 2 tablets (15 mg HB/650 mg APAP total dose) under 2 types of fed (high-fat and low-fat) and fasted conditions. Forty-eight subjects were enrolled and 40 subjects completed the study. Only subjects that completed all 3 study periods have been included in the PK evaluation.

Following a 10 hour overnight fast, subjects randomized to Treatment A consumed an entire standardized FDA high-fat breakfast (approximately 1,000±100 calories and approximately 50% from fat); those receiving Treatment B consumed an entire low-fat breakfast (approximately 800±80 calories and approximately 25% to 30% from fat). Breakfasts were consumed within 30 minutes prior to Hour 0 study drug administration. Subjects who could not consume the entire breakfast in the allotted time were dropped from the study. Subjects randomized to Treatment C were administered study drug under fasted conditions following an overnight fast of at least 10 hours. No food was allowed for the first 4 hours

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postdose. Blood samples were collected pre-dose (up to 60 minutes prior to dose), and at 15 min, 30 min, 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 18, 20, 24, 36 and 48 hours post-dose, and the resulting plasma samples were analyzed for Hydrocodone (HC) and APAP using a validated liquid chromatography-tandem mass spectrometry assay with a linear range of 0.100 to 50 ng/mL for HC and 100 to 15,000 ng/mL for APAP. Pharmacokinetic parameters, as detailed above in Example 2, were determined.

Tables 55 and 56 presents PK parameters for HC under the three treatment conditions, and FIG. 37 presents plasma HC concentration-time profiles for the treatments. Mean plasma concentration profiles of HC revealed that HC was rapidly absorbed under both fed (high and low fat meal) and fasted conditions. There was a slight lag (median 0.25 hours) when the formulation was administered after a low fat meal. The median of the time of observed maximum plasma concentrations (T_{max}) was 4 hours after administration under both the low fat and fasted conditions. Median T_{max} for HC under high fat conditions was significantly delayed, as compared to fasted conditions (6 hr vs. 4 hr; $P<0.05$). Average maximum plasma HC concentrations (C_{max}) were 23.09 ng/mL after a low fat breakfast, 21.66 ng/mL after a high fat breakfast, and 20.33 ng/mL under fasted conditions.

TABLE 55

Hydrocodone Pharmacokinetic Estimates (2 tablets of 7.5/325)				
Parameter	Treatment A Fed (High Fat) Mean (SD) (N = 31)	Treatment B Fed (Low Fat) Mean (SD) (N = 31)	Treatment C Fasted Mean (SD) (N = 31)	
AUC_{0-t} (ng · hr/mL)	301.50 (52.81)	299.72 (57.01)	280.10 (58.80)	
AUC_{0-inf} (ng · hr/mL)	303.66 (53.13)	301.95 (57.83)	282.94 (59.86)	
C_{max} (ng/mL)	21.66 (4.88)	23.09 (3.79)	20.33 (4.33)	
T_{max} (hr) ^a	6 (2-11)	4 (2-7)	4 (2-7)	
K_{el} (1/hr)	0.1273 (0.0207)	0.1218 (0.0202)	0.1110 (0.0194)	
t_{lag} (hr) ^a	0 (0-1.07)	0.25 (0-0.75)	0 (0-0.50)	
$t_{1/2}$ (hr)	5.58 (0.85)	5.85 (1.00)	6.43 (1.11)	

^aMedian (minimum-maximum).

A comparison of C_{max} showed that HC concentrations were 6% and 14% higher when the formulation was given under high fat (Treatment A) and low fat (Treatment B) conditions, compared to fasted conditions (Treatment C; see Table 55). The C_{max} for Treatment A was bioequivalent to both Treatments B (88%-99%) and C (101%-113%) as the 90% CIs for the geometric ratios were contained within 80% to 125% (see Table 56). The C_{max} observed for Treatment B was also bioequivalent to Treatment C (108%-122%). AUCs were approximately 7% higher when the formulation was administered under fed conditions (high and low fat), as compared to fasted conditions (Table 55). AUC for both Treatments A and B (high fat and low fat) were bioequivalent to Treatment C (fasted; 104%-112% and 103%-111% for AUC_{0-t} and 104%-112% and 103%-111% for AUC_{0-inf}) (Table 56). The apparent plasma terminal elimination half-life ($t_{1/2}$) for HC was similar when the formulation was administered under fed (5.58 hours) and fasted conditions (6.43 hours).

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TABLE 56

Hydrocodone Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment A/C Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment A/B Fed (High Fat)/ Fed (Low Fat)
AUC ₀₋₈	108.40	107.45	100.89
(ng · hr/mL) ^a	(104.44-112.51)	(103.53-111.52)	(97.22-104.69)
AUC _{0-inf}	108.11	107.17	100.88
(ng · hr/mL) ^a	(104.14-112.24)	(103.23-111.26)	(97.19-104.72)
C _{max} (ng/mL) ^a	106.66	114.75	92.95
	(100.54-113.15)	(108.16-121.73)	(87.64-98.59)

^aN = 40.

PK parameters for APAP are presented in Tables 57 and 58 and the plasma APAP concentration-time profiles are presented in FIG. 38. APAP was rapidly absorbed following administration under fed (high and low fat meals) and fasted conditions. There was a slight lag when the formulation was administered after a low fat breakfast (median lag time [t_{lag}] 0.25 hours). There was no lag in the absorption of APAP when administered following a high fast breakfast or after fasting. The time to C_{max} was significantly (P<0.05) longer when administered after a meal (high and low fat; median T_{max}=2 hours) than when administered under fasted conditions (median T_{max}=0.75 hour). Average C_{max} values for APAP were lower after a high (4,317 ng/mL) and low fat (4,122 ng/mL) meal than when administered under fasted conditions (5307 ng/mL). Geometric mean ratios for C_{max} following Treatments A and B were 20% to 22% lower than for Treatment C (Table 58). The 90% CIs for C_{max}, following Treatment A (75%-88%) and Treatment B (73%-83%) with reference to fasted state were outside the bioequivalent range of 80%-125%. The AUCs for APAP were almost identical when the formulation was administered under high fat, low fat, or fasted conditions. Comparison of geometric mean ratios of AUC₀₋₈ and AUC_{0-inf} for Treatments A (90% CI 100%-105% and 98%-103%) and B (90% CI 96%-101% and 97% to 103%) with those for Treatment C showed that treatments were bioequivalent. The t_{1/2} for APAP after the formulation was administered after a high or low fat meal (5 hours) was slightly shorter than when administered under fasted conditions (7 hours).

TABLE 57

APAP Pharmacokinetic Estimates (2 tablets of 7.5/325)			
Parameter	Treatment A Fed (High Fat) Mean (SD) (N = 31)	Treatment B Fed (Low Fat) Mean (SD) (N = 31)	Treatment C Fasted Mean (SD) (N = 31)
AUC ₀₋₈	33210.39	32415.11	32149.34
(ng · hr/mL)	(10402.75)	(9586.52)	(9431.97)
AUC _{0-inf}	34689.91	34092.21	34803.59
(ng · hr/mL)	(10672.37)	(9949.21)	(9635.34)
C _{max}	4317.00	4122.25	5307.00
(ng/mL)	(1185.08)	(877.19)	(1419.43)
T _{max} (hr) ^a	2 (0.25-6.05)	2 (0.75-7.00)	0.75 (0.25-5.00)
K _{el} (1/hr)	0.1444 (0.0470)	0.1317 (0.0356)	0.1072 (0.0402)
t _{lag} (hr) ^a	0 (0-0.63)	0.25 (0-0.50)	0.00 (0-0.25)
t _{1/2} (hr)	5.37 (2.02)	5.68 (1.68)	7.37 (2.77)

^aMedian (minimum-maximum).

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TABLE 58

APAP Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment A/C Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment A/B Fed (High Fat)/ Fed (Low Fat)
AUC ₀₋₈	102.70	100.74	101.94
(ng · hr/mL) ^a	(100.05-105.42)	(98.15-103.41)	(99.32-104.63)
AUC _{0-inf}	100.32	98.66	101.69
(ng · hr/mL) ^a	(97.71-103.01)	(96.09-101.30)	(99.04-104.40)
C _{max} (ng/mL) ^a	80.49	78.10	103.06
	(75.44-85.88)	(73.20-83.33)	(96.62-109.93)

^aN = 40.

In summary, total exposure (AUC) for HC was slightly increased (by about 7%) when the formulation was administered with food (after high- or low-fat meal); however, AUCs for HC were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted and high fat vs. low fat). Peak exposure (C_{max}) for HC was 6% and 14% higher under high fat and low-fat conditions, respectively, compared to fasted conditions. The C_{max} for HC after a high-fat meal and low fat meal were bioequivalent to fasted conditions. The AUCs for APAP were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted, and high fat vs. low fat). The peak exposure (C_{max}) for APAP was decreased by about 20% in fed (high- and low-fat) states as compared to the fasted state.

Example 18

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Hydrocodone/325 mg Acetaminophen—Single and Multiple Doses

An open-label, randomized, 3-period crossover study was performed to evaluate single and multiple dose pharmacokinetics, bioavailability, and safety of an extended release formulation containing 7.5 mg hydrocodone/325 mg acetaminophen under fasted conditions in normal, healthy subjects. (See example in Chart 2). The pharmacokinetics (PK) and bioavailability following administration of a 7.5 mg hydrocodone/325 mg acetaminophen tablet disclosed herein administered as either 1 or 2 tablets every 12 hours was compared to 1 immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen and administered every 6 hours (Q6h). The study also assessed the PK proportionality between the 1 tablet and 2 tablet dosing configurations of the 7.5 mg hydrocodone/325 mg acetaminophen tablet disclosed herein. In addition, the study evaluated the safety of the 1 tablet and 2 tablet dosing configurations of the 7.5 mg hydrocodone/325 mg acetaminophen tablet disclosed herein compared with immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen.

The subjects were randomly divided into three treatment options:

Treatment A: One tablet of the 7.5 mg hydrocodone/325 mg acetaminophen tablet disclosed herein administered orally under fasted conditions on Day 1 followed by 1 tablet given Q12h (beginning on Day 3 for a total of 9 doses).

Treatment B: Two tablets of the 7.5 mg hydrocodone/325 mg acetaminophen tablet disclosed herein administered orally under fasted conditions on Day 1 followed by 2 tablets given Q12h (beginning on Day 3 for a total of 9 doses).

Treatment C: One tablet of an immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen admin-

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istered orally Q6h for 2 doses under fasted conditions on Day 1 followed by 1 tablet given Q6h (beginning on Day 3 for a total of 18 doses).

The pharmacokinetic (PK) parameters of a single dose of hydrocodone and acetaminophen are presented below in Tables 59 and 60 respectively. The plasma concentrations of hydrocodone and acetaminophen are presented in FIGS. 39 and 40, respectively. The pharmacokinetic parameters demonstrate that the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen are dose proportional for both hydrocodone and acetaminophen. The pharmacokinetic profiles for hydrocodone showed an initial rapid rise in the concentrations of hydrocodone to provide a subject with the desired early onset of action (the median t_{lag} for the formulation disclosed herein is 0.08 hour and for the immediate release tablet it is 0.04 hour). The hydrocodone concentrations in the subjects that took the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen also fell slowly over a period of 12 hours.

Similarly, the pharmacokinetic profiles for acetaminophen showed an initial rapid rise in the concentrations of acetaminophen to provide the desired early onset of action (the median t_{lag} = 0 hr for the formulation disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen, which is the same as the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen). The acetaminophen concentrations achieved by the formulation disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen fell slowly, reaching levels that were lower than the immediate release tablet at around 12 hours, showing the desired "time off" from acetaminophen.

TABLE 59

Single Dose PK Parameters for Hydrocodone (Mean \pm SD)			
PK Parameters	One Tablet (7.5 HC/325 APAP) Treatment A	Two Tablets (7.5 HC/325 APAP) Treatment B	Commercially-available immediate release product (7.5 HC/325 APAP) Treatment C
C_{max} (ng/mL)	8.98 (2.02)	17.53 (3.69)	24.48 (5.69)
AUC_t (ng \cdot hr/mL)	122.43 (30.53)	248.48 (63.22)	254.39 (63.21)
AUC_{inf} (ng \cdot hr/mL)	124.24 (30.63)	251.20 (63.57)	256.24 (63.71)
t_{lag} (hr)	0.12 (0.14)	0.08 (0.13)	0.04 (0.09)
T_{max}^* (hr)	8.00 (0.25-6.00)	3.00 (0.25-2.00)	3.00 (0.25-8.00)
$T_{1/2}$ (hr)	6.26 (1.41)	6.41 (1.09)	5.37 (0.83)

* T_{max} values: median (range)

TABLE 60

Single Dose PK Parameters for Acetaminophen (Mean \pm SD)			
PK Parameters	One Tablet (7.5 HC/325 APAP) Treatment A	Two Tablets (7.5 HC/325 APAP) Treatment B	Commercially-available immediate release product (7.5 HC/325 APAP) Treatment C
C_{max} (ng/mL)	2604.55 (925.57)	5432.05 (1793.44)	4912.05 (1647.69)
AUC_t (ng \cdot hr/mL)	13248.82 (3889.65)	28593.91 (8400.40)	27928.74 (9086.86)

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TABLE 60-continued

Single Dose PK Parameters for Acetaminophen (Mean \pm SD)			
PK Parameters	One Tablet (7.5 HC/325 APAP) Treatment A	Two Tablets (7.5 HC/325 APAP) Treatment B	Commercially-available immediate release product (7.5 HC/325 APAP) Treatment C
AUC_{inf} (ng \cdot hr/mL)	15124.65 (4179.45)	31049.83 (8899.91)	28993.63 (9243.85)
t_{lag} (hr)	0.06 (0.11)	0.02 (0.07)	0.01 (0.04)
T_{max}^* (hr)	0.50 (0.25-6.00)	0.50 (0.25-2.00)	0.50 (0.25-8.00)
$T_{1/2}$ (hr)	7.73 (2.88)	8.32 (4.34)	4.29 (1.40)

* T_{max} values: median (range)

As shown below in Table 61, the 90% Confidence Intervals for all the pharmacokinetic parameters for hydrocodone dosed as a single dose of either one tablet or two tablets of the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen were contained within the 80-125% bioequivalence range for the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen. Similarly, as shown below in Table 62, the 90% Confidence Intervals for all the pharmacokinetic parameters for acetaminophen dosed as a single dose of either one tablet or two tablets of the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen were contained within the 80-125% bioequivalence range for the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen. However, the c_{max} values for both dosing configurations for the formulations disclosed herein were lower as compared to the immediate release product.

TABLE 61

Single Dose Bioequivalence Parameters for Hydrocodone				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
One Tablet	C_{max}	73.53	70.46	76.74
	AUC_t	96.2	92.33	100.23
	AUC_{inf}	96.97	93.10	100.99
	C_{max}	71.86	68.85	74.99
	AUC_t	97.59	93.66	101.68
	AUC_{inf}	97.96	94.06	102.03
Reference: Two tablets of the 7.5 mg HC/325 mg APAP				
Two Tablets	C_{max}	102.33	98.05	106.80
	AUC_t	98.58	94.61	102.71
	AUC_{inf}	98.98	95.04	103.09

TABLE 62

Single Dose Bioequivalence Parameters for Acetaminophen				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
One Tablet	C_{max}	105.34	97.98	113.25
	AUC_t	95.16	91.89	98.55
	AUC_{inf}	104.99	101.17	108.95

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TABLE 62-continued

Single Dose Bioequivalence Parameters for Acetaminophen				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
Two Tablets	C_{max}	110.78	103.04	119.10
	AUC_t	102.62	99.10	106.28
	AUC_{inf}	107.42	103.52	111.48
	Reference: Two tablets of the 7.5 mg HC/325 mg APAP			
One Tablet	C_{max}	95.09	88.45	102.24
	AUC_t	92.73	89.54	96.03
	AUC_{inf}	97.73	94.18	101.42

The pharmacokinetic (PK) parameters of multiple doses of hydrocodone and acetaminophen are presented below in Tables 63 and 64, respectively. The plasma concentrations of hydrocodone and acetaminophen are presented in FIGS. 41 and 42, respectively. The pharmacokinetic parameters demonstrate that the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen are dose proportional for both hydrocodone and acetaminophen. No differences were observed in dose-normalized C_{max}^{ss} , C_{min}^{ss} , AUC_{0-12}^{ss} , C_{av}^{ss} , and fluctuation of hydrocodone and acetaminophen following administration of the formulation disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen as either 1-tablet or 2-tablet dosing configurations, or the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen. For acetaminophen, the 1-tablet, 2-tablet and immediate release tablet had the same (0.5 hr) median T_{max}^{ss} . For hydrocodone, the median T_{max}^{ss} of the formulation disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen (dosed as either 1 and 2 tablets) was 2 hours while the median T_{max}^{ss} for the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen was 1 hour. No difference was observed in the swing of hydrocodone for the formulation disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen dosed as either 1 and 2-tablet and the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen. In the case of acetaminophen, the swing was partially out of the range to demonstrate no difference (107.33-132.50).

TABLE 63

Multiple Dose PK Parameters for Hydrocodone (Mean \pm SD)			
PK Parameters	One Tablet (7.5 HC/325 APAP)	Two Tablets (7.5 HC/325 APAP)	Commercially-available immediate release product (7.5 HC/325 APAP)
	Treatment A	Treatment B	Treatment C
C_{max}^{ss} (ng/mL)	15.57 (3.85)	30.54 (6.87)	33.80 (8.74)
C_{min}^{ss} (ng/mL)	6.49 (2.41)	13.38 (4.12)	14.13 (4.67)
C_{avg}^{ss} (ng/mL)	11.20 (3.16)	22.54 (5.36)	22.38 (5.82)
AUC_{0-12}^{ss} (ng · hr/mL)	134.36 (37.91)	270.52 (64.29)	268.57 (69.87)
T_{max}^{ss} (hr)	146.00 (144.50-150.00)	146.00 (144.50-150.00)	145.00 (144.50-142.00)
Swing	1.53 (1.00)	1.37 (1.42)	1.53 (3.16)
Fluctuation (%)	83.76 (19.00)	77.54 (16.70)	90.60 (3054)

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TABLE 63-continued

Multiple Dose PK Parameters for Hydrocodone (Mean \pm SD)			
PK Parameters	One Tablet (7.5 HC/325 APAP)	Two Tablets (7.5 HC/325 APAP)	Commercially-available immediate release product (7.5 HC/325 APAP)
	Treatment A	Treatment B	Treatment C
Accumulation Index	1.43 (0.20)	1.43 (0.20)	1.23 (0.29)

*Tmax values: median (range)

TABLE 64

Multiple Dose PK Parameters for Acetaminophen (Mean \pm SD)			
PK Parameters	One Tablet (7.5 HC/325 APAP)	Two Tablets (7.5 HC/325 APAP)	Commercially-available immediate release product (7.5 HC/325 APAP)
	Treatment A	Treatment B	Treatment C
C_{min}^{ss} (ng/mL)	464.89 (166.72)	844.68 (293.41)	893.86 (310.09)
C_{avg}^{ss} (ng/mL)	1169.43 (316.86)	2238.75 (577.32)	2267.63 (592.95)
AUC_{0-12}^{ss} (ng · hr/mL)	14033.21 (3802.32)	26864.94 (6927.89)	27211.55 (7115.37)
T_{max}^{ss} (hr)	144.5 (144.25-148.00)	144.5 (144.25-146.00)	144.5 (144.25-152.00)
Swing	6.43 (0.96)	6.78 (0.44)	5.76 (2.80)
Fluctuation (%)	237.58 (85.70)	237.66 (74.05)	211.43 (76.05)
Accumulation Index	1.28 (0.21)	1.21 (0.17)	1.05 (0.06)

*Tmax values: median (range)

As shown below in Table 65, the 90% Confidence Intervals for all the pharmacokinetic parameters for hydrocodone dosed as multiple doses of either one tablet or two tablets of the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen were contained within the 80-125% bioequivalence range for the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen. Similarly, as shown below in Table 66, the 90% Confidence Intervals for all the pharmacokinetic parameters (except the swing) for acetaminophen dosed as multiple doses of either one tablet or two tablets of the formulations disclosed herein containing 7.5 mg hydrocodone/325 mg acetaminophen were contained within the 80-125% bioequivalence range for the immediate release tablet containing 7.5 mg hydrocodone/325 mg acetaminophen.

TABLE 65

Multiple Dose Bioequivalence Parameters for Hydrocodone				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
One Tablet	C_{max}^{ss}	92.46	89.07	95.98
	C_{min}^{ss}	91.22	87.61	94.98
	C_{avg}^{ss}	99.7	96.85	102.64
	AUC_{0-12}^{ss}	99.71	96.85	102.65
	Swing	103.98	97.05	111.4
	Fluctuation	95.13	90.54	99.94

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TABLE 65-continued

Multiple Dose Bioequivalence Parameters for Hydrocodone				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
Two Tablets	$C_{max}(ss)$	90.91	87.58	94.38
	$C_{min}(ss)$	95.33	91.56	99.26
	$C_{avg}(ss)$	101.15	98.25	104.14
	$AUC_{0-12}(ss)$	101.15	98.26	104.14
	Swing	93.88	87.62	100.58
	Fluctuation	88.47	84.21	92.95
Reference: Two tablets of the 7.5 mg HC/325 mg APAP				
One Tablet	$C_{max}(ss)$	101.7	97.97	105.57
	$C_{min}(ss)$	95.69	91.9	99.64
	$C_{avg}(ss)$	98.57	95.74	101.48
	$AUC_{0-12}(ss)$	98.57	95.75	101.48

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TABLE 66-continued

Multiple Dose Bioequivalence Parameters for Acetaminophen				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
	Swing	94.29	84.86	104.76
	Fluctuation	98.89	91.11	107.32

Example 19

Partial Areas Under the Curve for Hydrocodone and Acetaminophen

A cross-study comparison of the partial AUCs for acetaminophen following oral administration of the pharmaceutical compositions described in Treatment A of Example 16, and Treatment C of Example 17 was performed. These results are summarized in Tables 67 and 68. Additionally, the partial AUCs for hydrocodone were determined and are summarized in Tables 69.

TABLE 67

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.						
Study	AUC_{0-1h}	AUC_{1-12h}	AUC_{12-36h}	$AUC_{0-1.27h}$	$AUC_{1.27-36h}$	AUC_{0-t}
Treatment A (Ex. 16)	3276.62	20624.53	7774.64	3816.89	27858.88	30618.62
Treatment C (Ex. 17)	3264.68	22299.56	8284.15	4428.19	20420.21	32441.45

TABLE 65-continued

Multiple Dose Bioequivalence Parameters for Hydrocodone				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
	Swing	110.76	103.38	118.66
	Fluctuation	107.52	102.34	112.96

TABLE 68

Percent of the partial AUC compared to AUC_{0-t}		
Study	AUC_{1-12h}	AUC_{12-36h}
Treatment A (Ex. 16)	67%	25%
Treatment C (Ex. 17)	69%	26%

TABLE 66

Multiple Dose Bioequivalence Parameters for Acetaminophen				
Test	PK Parameter	LSM	90% CI	
			Lower	Upper
Immediate Release Tablet				
One Tablet	$C_{max}(ss)$	113.39	105.69	121.66
	$C_{min}(ss)$	102.92	98.12	107.95
	$C_{avg}(ss)$	102.81	100.19	105.49
	$AUC_{0-12}(ss)$	102.81	100.19	105.49
	Swing	112.44	101.2	124.93
	Fluctuation	112.56	103.72	122.17
Two Tablets	$C_{max}(ss)$	109.25	101.83	117.21
	$C_{min}(ss)$	94.27	89.87	98.88
	$C_{avg}(ss)$	98.76	96.25	101.33
	$AUC_{0-12}(ss)$	98.76	96.25	101.33
	Swing	119.25	107.33	132.5
	Fluctuation	113.83	104.88	123.54
Reference: Two tablets of the 7.5 mg HC/325 mg APAP				
One Tablet	$C_{max}(ss)$	103.79	96.74	111.36
	$C_{min}(ss)$	109.17	104.08	114.51
	$C_{avg}(ss)$	104.1	101.45	106.82
	$AUC_{0-12}(ss)$	104.1	101.45	106.82

TABLE 69

Mean (SD) Parameter Estimates for Partial AUCs for Hydrocodone.			
Study	AUC_{0-t} (ng · h/mL)	$AUC_{0-2.44h}$ (ng · h/mL)	$AUC_{2.44-36h}$ (ng · h/mL)
Treatment A (Ex. 16)	254.16 (71.57)	26.33 (8.70)	227.93 (65.32)
Treatment C (Ex. 17)	280.08 (59.58)	27.41 (9.34)	246.25 (52.99)

Further, it was determined that T_{max} for an immediate release tablet containing 7.5 mg hydrocodone and 325 mg acetaminophen plus two standard deviations was about 3 hr. Some of the partial AUCs of the pharmaceutical formulation described herein were determined in accordance with this time interval.

The bioequivalence determinations between two tablets of a pharmaceutical composition described herein, each containing 7.5 mg hydrocodone and 325 mg acetaminophen (in fed and fasted states) and an immediate release tablet containing 7.5 mg hydrocodone and 325 mg acetaminophen can be found in Tables 70 and 71.

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TABLE 70

Bioequivalence Determination for Acetaminophen			
Parameter	LSM Ratio	90% CI	
		Lower	Upper
Ln (AUC _{0-1.27h})	103.62	87.18	123.16
Ln (AUC _{1.27-3.6h})	93.32	83.11	104.78
Ln (AUC _{0-t})	94.52	84.34	105.93

TABLE 71

Bioequivalence Determination for Hydrocodone			
Parameter	LSM Ratio	90% CI	
		Lower	Upper
Ln (AUC _{0-2.44h})	91.49	82.77	101.13
Ln (AUC _{2.44-3.6h})	96.78	83.19	112.61
Ln (AUC _{0-t})	89.71	81.51	98.74

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Example 20

In Vitro Dissolution of Controlled-Release Bilayer Tablets Containing 7.5 mg Oxycodone and 325 mg Acetaminophen Performed at a 100 rpm Paddle Speed

Three batches of bilayer formulations described herein were prepared, each containing a total of 7.5 mg of oxycodone HCl and a total of 325 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the oxycodone HCl was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations of each batch were determined in a USP Type II apparatus. Six tablets from each batch were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 100±4 rpm, and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and oxycodone from each batch are described in Table 72.

TABLE 72

Release rate data of bilayer tablets (7.5 mg oxycodone HCl; 325 mg acetaminophen) using a 100 rpm dissolution method.								
Time (Hours)	Oxycodone HCl				Acetaminophen			
	Mean (%)	RSD	Min (%)	Max (%)	Mean (%)	RSD	Min (%)	Max (%)
Batch 1								
0.25	31.7	2.1	30.6	32.5	51.8	1.4	50.9	53.1
0.5	37.1	1.3	36.3	37.8	54.3	1.3	53.5	55.6
1.0	45.4	1.0	44.9	46.0	58.6	1.2	57.7	60.1
2.0	58.5	1.3	57.4	59.7	66.0	1.2	64.8	67.7
4.0	78.6	1.7	76.8	80.5	78.5	1.5	77.0	80.6
6.0	92.2	1.8	90.0	94.7	88.0	1.6	86.0	90.3
8.0	99.5	1.8	97.4	102.7	93.8	1.5	91.8	96.3
12.0	101.7	1.4	99.7	104.3	96.1	1.0	94.9	98.2
Batch 2								
0.25	31.6	3.5	29.6	34.0	52.1	4.0	48.8	55.8
0.5	37.2	3.2	34.9	39.9	54.5	3.8	51.4	58.3
1.0	45.4	3.3	42.4	48.3	59.1	3.5	56.0	63.1
2.0	58.9	1.7	57.3	61.1	66.4	3.0	63.6	70.0
4.0	79.1	1.5	77.7	81.5	78.7	2.5	75.4	81.8
6.0	93.1	1.3	91.5	95.8	87.7	2.2	84.4	90.7
8.0	100.2	1.2	98.7	102.3	93.5	1.9	90.4	96.2
12.0	102.7	1.3	100.4	104.4	95.6	2.0	92.6	98.4
Batch 3								
0.25	30.4	1.6	29.3	31.0	52.2	2.3	49.6	54.2
0.5	35.7	1.6	34.2	36.7	54.6	2.3	52.0	56.6
1.0	43.5	1.8	42.0	45.1	58.6	2.2	56.0	60.8
2.0	56.1	1.9	54.4	58.0	65.5	2.1	63.1	68.0
4.0	75.4	1.8	73.3	77.6	77.3	2.0	74.8	80.0
6.0	88.9	1.7	86.1	91.4	86.5	2.2	83.7	90.1
8.0	97.0	1.5	94.7	99.8	93.0	2.1	90.1	96.8
12.0	100.4	1.1	98.7	102.4	96.5	1.6	93.2	98.3

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Example 21

In Vitro Dissolution of Controlled-Release Bilayer Tablets Comprising 7.5 mg Hydrocodone and 325 mg Acetaminophen Performed at a 100 rpm Paddle Speed

Three batches of bilayer formulations described herein were prepared, each containing a total of 7.5 mg of hydrocodone bitartrate and a total of 325 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the hydrocodone bitartrate was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® N-60K was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations of each batch were determined in a USP Type II apparatus. Six tablets from each batch were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 100±4 rpm, and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and hydrocodone from each batch are described in Table 73.

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Example 22

In Vitro Dissolution of Controlled-Release Bilayer Tablets Comprising 7.5 mg Hydrocodone and 325 mg Acetaminophen Performed at a 150 rpm Paddle Speed

Dissolution studies were performed on fast-release, medium-release, and slow-release pharmaceutical formulations described herein containing 7.5 mg hydrocodone and 325 mg acetaminophen.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel that contained 900 mL of (helium sparged) 0.1 N HCl that was heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The results of these dissolution studies are summarized in Table 74 and FIGS. 43 and 44.

TABLE 73

Release rate data of bilayer tablets (7.5 mg hydrocodone bitartrate; 325 mg acetaminophen) using a 100 rpm dissolution method.								
Time (Hours)	Hydrocodone Bitartrate				Acetaminophen			
	Mean (%)	RSD	Min (%)	Max (%)	Mean (%)	RSD	Min (%)	Max (%)
Batch 1								
0.25	31.4	6.3	27.1	33.6	52.7	5.1	46.7	54.6
0.5	36.5	3.6	34.1	38.6	55.5	2.5	52.2	56.8
1.0	43.7	2.1	42.2	45.2	59.1	1.4	57.3	60.1
2.0	54.5	1.7	53.0	56.6	64.7	0.9	63.8	65.8
4.0	70.9	1.3	69.4	72.9	74.0	0.8	73.1	75.2
6.0	83.0	1.5	81.1	85.3	81.8	0.9	80.6	83.3
8.0	91.9	1.5	89.7	93.8	88.4	0.9	87.4	89.9
12.0	100.5	1.4	98.1	102.5	96.1	0.8	94.9	97.2
Batch 2								
0.25	30.8	3.0	29.6	32.5	53.6	1.7	52.4	55.1
0.5	35.6	2.1	34.5	37.0	55.8	1.4	54.9	57.1
1.0	42.4	2.3	40.7	44.5	59.1	1.3	58.4	60.6
2.0	52.7	2.1	51.6	54.8	64.6	1.3	63.9	66.5
4.0	69.0	2.0	67.4	71.5	73.9	1.3	72.8	76.2
6.0	81.8	1.7	79.5	83.5	82.4	1.4	80.9	85.1
8.0	90.3	1.5	87.9	92.5	88.6	1.6	86.6	91.9
12.0	98.9	1.6	96.0	101.0	96.5	1.5	94.4	99.8
Batch 3								
0.25	31.7	3.2	29.7	33.6	52.7	2.5	49.9	54.9
0.5	36.4	2.8	34.7	38.2	55.1	2.0	53.1	56.9
1.0	43.5	2.3	42.1	45.1	58.7	1.8	57.5	60.7
2.0	54.5	2.4	52.9	56.5	64.5	1.7	63.3	66.8
4.0	70.2	2.5	68.2	72.7	73.7	1.7	72.1	76.4
6.0	81.8	2.2	79.8	85.6	81.3	1.6	79.2	84.3
8.0	90.5	2.3	88.0	95.1	87.8	1.6	85.5	91.0
12.0	98.9	1.9	97.1	103.0	95.2	1.4	92.9	98.2

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TABLE 74

Mean acetaminophen and hydrocodone dissolution data.						
Time (hr)	Fast (%) (RSD)		Medium (%) (RSD)		Slow (%) (RSD)	
	APAP	Hydro-codone	APAP	Hydro-codone	APAP	Hydro-codone
0.08	52.6(2.2)	26.3(4.1)	52.4(2.7)	28.4(4.3)	52.2(2.1)	28.8(4.0)
0.25	55.8(2.0)	34.3(2.1)	54.4(2.7)	33.4(2.9)	54.2(1.7)	33.8(2.8)
0.5	58.9(1.9)	41.2(1.4)	56.9(2.5)	38.6(2.4)	56.2(1.5)	38.2(3.3)
1.0	64.0(1.8)	51.1(1.4)	60.9(2.3)	46.8(1.9)	59.5(1.5)	45.2(3.5)
2.0	72.8(1.6)	65.9(2.0)	67.9(2.0)	59.7(2.1)	65.0(1.4)	56.3(3.5)
4.0	87.0(1.8)	86.7(2.6)	79.8(1.6)	79.6(2.1)	74.6(1.4)	74.0(2.6)
8.0	98.5(1.1)	100.7(1.2)	93.9(1.0)	99.7(1.9)	88.2(1.4)	94.9(2.4)
12.0	97.9(1.2)	100.5(1.5)	96.9(0.8)	102.9(1.6)	95.6(1.7)	103.0(2.4)
18.0	96.8(1.2)	100.3(1.6)	96.1(0.8)	102.8(1.7)	97.0(1.5)	104.6(2.1)

Example 23

Varying Polyox Grades Comprising 25% by Weight
of the Extended Release Portion of Bilayer
Formulations Containing Oxycodone

Single layer tablet formulations containing only the extended release portion were prepared, each tablet containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for the bilayer tablet and 60% of the total oxycodone HCl for the bilayer tablet. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 25% by weight of the ER portion, and therefore, the tablet weight. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the tablet of ER portion. In a third formulation, POLYOX® N-60K was employed as the extended release component in an amount of 25% by weight of the tablet or ER portion.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the Polyox 205 was 17 hrs; the final time point for the Polyox 1105 was 15 hrs; and the final time point for the Polyox N60k was 18 hrs and 40 minutes. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 45 and 46, respectively. This data represents dissolution for the ER portion with the IR data theoretically added. These figures demonstrate that as the average molecular weight of the POLYOX® extended release component increases, the rate of dissolution at each time point decreases. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 59%, about 56%, and about 55% acetaminophen after 15 minutes, respectively; about 63%, about 59%, and about 57% acetaminophen after 30 minutes, respectively; about 69%, about 64%, and about 61% acetaminophen after 1 hr, respectively; about 78%, about 73%, and about 67% acetaminophen after 2 hr, respectively; about 91%,

about 87%, and about 76% acetaminophen after 4 hr, respectively; about 97%, about 95%, and about 84% acetaminophen after 6 hr, respectively; and about 98%, about 97%, and about 90% acetaminophen after 8 hr, respectively.

The same general trend of a decreased release rate with a higher molecular weight POLYOX® grade was also observed for the oxycodone. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 53%, about 50%, and about 48% oxycodone after 15 minutes, respectively; about 60%, about 56%, and about 53% oxycodone after 30 minutes, respectively; about 68%, about 63%, and about 59% oxycodone after 1 hr, respectively; about 80%, about 75%, and about 67% oxycodone after 2 hr, respectively; about 94%, about 91%, and about 80% oxycodone after 4 hr, respectively; about 100%, about 98%, and about 89% oxycodone after 6 hr, respectively; and about 100%, about 99%, and about 95% oxycodone after 8 hr, respectively.

Example 24

Varying Polyox Grades Comprising 45% by Weight
of the Extended Release Portion of Bilayer
Formulations Containing Oxycodone

Single layer formulations containing only the extended release portion described herein were prepared, each tablet containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for a bilayer tablet and 60% of the total oxycodone HCl for a bilayer tablet. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a third formulation, POLYOX® N-60K was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. The other excipients in the extended release portion were microcrystalline cellulose, sprss B825, citric acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate.

Dissolution profiles for the three above-described formulations were determined in USP Type II apparatus. Six tablets of each formulation were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. through 12 hr. The bath vessel was covered with a low evaporation vessel

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cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the Polyox 205 was 17 hours; the final time point for Polyox 1105 was 17.5 hours; and the final time point for Polyox N60k was 23.5 hours. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 47 and 48, respectively. This data represents dissolution for the extended release portion with the immediate release data theoretically added. Consistent with the results of Example 23, the rate of dissolution at each time point decreases as the molecular weight of POLYOX® increases. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 53%, about 53%, and about 53% acetaminophen after 15 minutes, respectively; about 56%, about 55%, and about 54% acetaminophen after 30 minutes, respectively; about 61%, about 60%, and about 57% acetaminophen after 1 hr, respectively; about 70%, about 67%, and about 63% acetaminophen after 2 hr, respectively; about 85%, about 81%, and about 71% acetaminophen after 4 hr, respectively; about 95%, about 90%, and about 79% acetaminophen after 6 hr, respectively; about 99%, about 95%, and about 85% acetaminophen after 8 hr, respectively; and about 99%, about 96% and about 93% acetaminophen after 12 hr.

The formulations containing POLYOX® 205, 1105, and N-60K also released about 47%, about 47%, and about 46% oxycodone after 15 minutes, respectively; about 51%, about 50%, and about 49% after 30 minutes, respectively; about 59%, about 56%, and about 53% oxycodone after 1 hr, respectively; about 70%, about 67%, and about 62% oxycodone after 2 hr, respectively; about 88%, about 83%, and about 74% oxycodone after 4 hr, respectively; about 99%, about 93%, and about 83% oxycodone after 6 hr, respectively; and about 100%, about 97%, and about 90% oxycodone after 8 hr, respectively.

Example 25

Varying the Concentrations of a Specific Polyox Grade in the Extended Release Portion of Bilayer Formulations Containing Oxycodone

The data from Examples 23 and 24 indicate that an increase in the amount of POLYOX® in the pharmaceutical composition retards the release of oxycodone and acetaminophen from the pharmaceutical composition. To confirm this observation, single layer ER formulations described herein were prepared, each containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for the bilayer tablet and 60% of the total oxycodone for the bilayer tablet. In a first formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the tablet or ER portion. In a second formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 35% by weight of the tablet or ER portion. In a third formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a fourth formulation, POLYOX® 1105 was employed as the extended release component in an amount of 55% by weight of the tablet or ER portion. The amount of the microcrystalline cellulose in the four formulations was adjusted to account for the differing amounts of POLYOX® 1105 in each formulation. The other excipients in the extended release portion were 8825, citric

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acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate. However, the percentages for all the other excipients remained the same for each formulation, and were consistent with the percentages used in Example 24.

Dissolution profiles for the above-described formulations were determined in USP Type II apparatus. Six tablets of each formulation were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the 25%, 35%, 45%, and 55% formulations was 15 hr, 15 hr, 17.5 hr, and 17.5 hr, respectively. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 49 and 50, respectively. These profiles confirm that as the amount of POLYOX® 1105 used in the pharmaceutical formulations increase, the release rate of the acetaminophen and oxycodone generally decreases. For example, the formulations containing 25%, 45%, and 55% POLYOX® 1105 had released about 56%, about 53%, and about 53% acetaminophen after 15 minutes, respectively; about 59%, about 56%, about 55%, and about 55% acetaminophen after 30 minutes, respectively; about 64%, about 61%, about 60%, and about 59% acetaminophen after 1 hr, respectively; about 73%, about 70%, about 67%, and about 66% acetaminophen after 2 hr, respectively; about 87%, about 84%, about 81%, and about 79% acetaminophen after 4 hr, respectively; about 95%, about 93%, about 90%, and about 89% acetaminophen after 6 hr, respectively; about 97%, about 97%, about 95%, and about 95% acetaminophen after 8 hr, respectively; and about 97%, about 97%, about 96%, and about 98% acetaminophen after 12 hr, respectively.

Similar trends were observed for the cumulative release of oxycodone. However, there was no observable difference in the release of oxycodone from the formulations containing 45% and 55% POLYOX® 1105. For example, the formulations containing 25%, 45%, and 55% POLYOX® 1105 had released about 50%, about 47%, and about 45% oxycodone after 15 minutes, respectively; about 56%, about 51%, about 50%, and about 50% oxycodone after 30 minutes, respectively; about 63%, about 58%, about 56%, and about 56% oxycodone after 1 hr, respectively; about 75%, about 70%, about 67%, and about 66% oxycodone after 2 hr, respectively; about 91%, about 87%, about 83%, and about 82% oxycodone after 4 hr, respectively; about 98%, about 96%, about 93%, and about 93% oxycodone after 6 hr, respectively; about 99%, about 99%, about 97%, and about 98% oxycodone after 8 hr, respectively; and about 99%, about 100%, about 97%, and about 100% oxycodone after 12 hr, respectively.

Example 26

Varying Polyox Grades Comprising 25% by Weight of the Extended Release Portion of Bilayer Formulations Containing Hydrocodone

Bilayer formulations described herein were prepared, each containing a total of 15 mg of hydrocodone bitartrate and a total of 500 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the hydrocodone

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bitartrate was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 25% by weight of the ER portion. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the ER portion. In a third formulation, POLYOX® N-12K was employed as the extended release component in an amount of 25% by weight of the ER portion. In a fourth formulation, POLYOX® N-60K was employed as the extended release component in an amount of 25% by weight of the ER portion. In a fifth formulation, POLYOX® 301 was employed as the extended release component in an amount of 25% by weight of the ER portion. The other excipients in the extended release portion were microcrystalline cellulose, spress B825, citric acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate.

Dissolution profiles for the five above-described compositions were determined in a USP Type II apparatus. Five tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. ± 0.5° C. The mixture was stirred at 150 ± 6 rpm, and the temperature was maintained at 37° C. ± 0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, and 18 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and hydrocodone from these compositions are shown in FIGS. 51 and 52, respectively. These figures demonstrate that as the average molecular weight of the POLYOX® extended release component increases, the rate of dissolution at each time point decreases. For example, the formulations containing POLYOX® 205, 1105, N-12K, N-60K, and 301 had released about 59%, about 58%, about 56%, about 55%, and about 52% acetaminophen after 15 minutes, respectively; about 62%, about 61%, about 58%, about 57%, and about 56% acetaminophen after 30 minutes, respectively; about 68%, about 66%, about 63%, about 61%, and about 60% acetaminophen after 1 hr, respectively; about 78%, about 76%, about 71%, about 67%, and about 65% acetaminophen after 2 hr, respectively; about 92%, about 90%, about 83%, about 76%, and about 73% acetaminophen after 4 hr, respectively; about 98%, about 97%, about 92%, about 84%, and about 79% acetaminophen after 6 hr, respectively; about 99%, about 98%, about 96%, about 90%, and about 85% acetaminophen after 8 hr, respectively; about 98%, about 97%, about 96%, about 97%, and about 92% acetaminophen after 12 hr, respectively; and about 98%, about 97%, about 96%, about 97%, and about 97% acetaminophen after 18 hr, respectively.

The same general trend of a decreased release rate with a higher molecular weight POLYOX® grade was also observed for the hydrocodone bitartrate. For example, the formulations containing POLYOX® 205, 1105, N-12K, N-60K, and 301 had released about 38%, about 39%, about 39%, about 34%, and about 32% hydrocodone bitartrate after 15 minutes, respectively; about 48%, about 47%, about 46%, about 41%, and about 39% hydrocodone bitartrate after 30 minutes, respectively; about 60%, about 57%, about 55%, about 49%, and about 47% hydrocodone bitartrate after 1 hr, respectively; about 76%, about 72%, about 68%, about 60%, and about 58% hydrocodone bitartrate after 2 hr, respectively; about 96%, about 93%, about 87%, about 77%, and about 73% hydrocodone bitartrate after 4 hr, respectively; about 105%,

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about 102%, about 99%, about 89%, and about 83% hydrocodone bitartrate after 6 hr, respectively; about 105%, about 102%, about 103%, about 97%, and about 91% hydrocodone bitartrate after 8 hr, respectively; about 105%, about 102%, 103%, about 104%, and about 100% hydrocodone bitartrate after 12 hr, respectively; and about 106%, about 103%, about 104%, about 104%, and about 104% hydrocodone bitartrate after 18 hr, respectively.

Example 27

Varying Polyox Grades Comprising 45% by Weight of the Extended Release Portion of Bilayer Formulations Containing Hydrocodone

The release rate studies described in Example 26 were repeated, except that the five bilayer formulations were prepared such that they included POLYOX® 205, 1105, N-12K, N-60K, and 301 in an amount of 45% by weight of the ER portion.

The cumulative release profiles of acetaminophen and hydrocodone from these compositions are shown in FIGS. 53 and 54, respectively. Consistent with the results of Example 26, the rate of dissolution at each time point generally decreases as the average molecular weight of POLYOX® increases. For example, the formulations containing POLYOX® 205, 1105, N-12K, N-60K, and 301 had released about 55%, about 53%, about 55%, about 54%, and about 54% acetaminophen after 15 minutes, respectively; about 57%, about 56%, about 57%, about 55%, and about 56% acetaminophen after 30 minutes, respectively; about 62%, about 60%, about 60%, about 58%, and about 59% acetaminophen after 1 hr, respectively; about 70%, about 68%, about 67%, about 64%, and about 63% acetaminophen after 2 hr, respectively; about 84%, about 81%, about 78%, about 72%, and about 70% acetaminophen after 4 hr, respectively; about 95%, about 91%, about 87%, about 80%, and about 77% acetaminophen after 6 hr, respectively; about 99%, about 96%, about 93%, about 86%, and about 82% acetaminophen after 8 hr, respectively; about 99%, about 98%, about 99%, about 95%, and about 90% acetaminophen after 12 hr, respectively; and about 98%, about 97%, about 98%, about 99%, and about 96% acetaminophen after 18 hr, respectively.

The same general trend of a decreased release rate with a higher molecular weight POLYOX® grade was also observed for the hydrocodone bitartrate. For example, the formulations containing POLYOX® 205, 1105, N-12K, N-60K, and 301 had released about 33%, about 33%, about 32%, about 31%, and about 32% hydrocodone bitartrate after 15 minutes, respectively; about 39%, about 39%, about 38%, about 36%, and about 37% hydrocodone bitartrate after 30 minutes, respectively; about 48%, about 48%, about 46%, about 43%, and about 43% hydrocodone bitartrate after 1 hr, respectively; about 63%, about 63%, about 59%, about 54%, and about 53% hydrocodone bitartrate after 2 hr, respectively; about 85%, about 84%, about 79%, about 71%, and about 68% hydrocodone bitartrate after 4 hr, respectively; about 99%, about 97%, about 92%, about 84%, and about 79% hydrocodone bitartrate after 6 hr, respectively; about 102%, about 103%, about 100%, about 93%, and about 88% hydrocodone bitartrate after 8 hr, respectively; about 103%, about 104%, about 104%, about 102%, and about 98% hydrocodone bitartrate after 12 hr, respectively; and about 104%, about 103%, about 104%, about 105%, and about 103% hydrocodone bitartrate after 18 hr, respectively.

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Example 28

Varying the Concentrations of a Specific Polyox
Grade in the Extended Release Portion of Bilayer
Formulations Containing Hydrocodone

The data from Examples 26 and 27 indicate that an increase in the amount of POLYOX® in the pharmaceutical composition also retards release of the actives from the pharmaceutical composition. To confirm this observation, bilayer formulations described herein were prepared, each containing a total of 15 mg of hydrocodone bitartrate and a total of 500 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the hydrocodone bitartrate was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. In a first formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the ER portion. In a second formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 35% by weight of the ER portion. In a third formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

The cumulative release profiles of acetaminophen and hydrocodone bitartrate from these compositions are shown in FIGS. 55 and 56, respectively. These profiles confirm that as the amount of POLYOX® 1105 used in the pharmaceutical formulations increase, the release rate of the actives generally decreases. For example, the formulations containing 25%, 35%, and 45% POLYOX® 1105 had released about 58%, about 54%, and about 53% acetaminophen after 15 minutes, respectively; about 61%, about 56%, and about 56% acetaminophen after 30 minutes, respectively; about 66%, about 61%, and about 60% acetaminophen after 1 hr, respectively; about 76%, about 70%, and about 68% acetaminophen after 2 hr, respectively; about 90%, about 85%, and about 81% acetaminophen after 4 hr, respectively; about 97%, about 94%, and about 91% acetaminophen after 6 hr, respectively; about 98%, about 97%, and about 96% acetaminophen after 8 hr, respectively; about 97%, about 97%, and about 98% acetaminophen after 12 hr, respectively; and about 97%, about 96%, and about 97% acetaminophen after 18 hr, respectively.

Similar trends were observed for the cumulative release of hydrocodone bitartrate. For example, the formulations containing 25%, 35%, and 45% POLYOX® 1105 had released about 39%, about 34%, and about 33% hydrocodone bitartrate after 15 minutes, respectively; about 47%, about 39%, and about 39% hydrocodone bitartrate after 30 minutes, respectively; about 57%, about 49%, and about 48% hydrocodone bitartrate after 1 hr, respectively; about 72%, about 65%, and about 63% hydrocodone bitartrate after 2 hr, respectively; about 93%, about 88%, and about 84% hydrocodone bitartrate after 4 hr, respectively; about 102%, about 100%, about 97% hydrocodone bitartrate after 6 hr, respectively; about 102%, about 103%, and about 103% hydrocodone bitartrate after 8 hr, respectively; about 102%, about 104%, and about 104% hydrocodone bitartrate after 12 hr, respectively; and about 103%, about 103%, and about 103% hydrocodone bitartrate after 18 hr, respectively.

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Example 29

Varying the Concentrations of a Specific Polyox
Grade in the Extended Release Portion of Bilayer
Formulations Containing Hydrocodone

The release rate studies described in Example 28 were repeated, except that the three bilayer formulations were prepared such that they included POLYOX® N-60K instead of 1105.

The cumulative release profiles of acetaminophen and hydrocodone bitartrate from these compositions are shown in FIGS. 57 and 58, respectively. These profiles confirm that as the amount of POLYOX® N-60K used in the pharmaceutical formulations increase, the release rate of the actives generally decreases. For example, the formulations containing 25%, 35%, and 45% POLYOX® N-60K had released about 55%, about 54%, and about 54% acetaminophen after 15 minutes, respectively; about 57%, about 56%, and about 55% acetaminophen after 30 minutes, respectively; about 61%, about 60%, and about 58% acetaminophen after 1 hr, respectively; about 67%, about 65%, and about 64% acetaminophen after 2 hr, respectively; about 76%, about 74%, and about 72% acetaminophen after 4 hr, respectively; about 84%, about 82%, and about 80% acetaminophen after 6 hr, respectively; about 90%, about 88%, and about 86% acetaminophen after 8 hr, respectively; about 97%, about 96%, and about 95% acetaminophen after 12 hr, respectively; and about 97%, about 98%, and about 99% acetaminophen after 18 hr, respectively.

Similar trends were observed for the cumulative release of hydrocodone bitartrate. For example, the formulations containing 25%, 35%, and 45% POLYOX® N-60K had released about 34%, about 32%, and about 31% hydrocodone bitartrate after 15 minutes, respectively; about 41%, about 37%, and about 36% hydrocodone bitartrate after 30 minutes, respectively; about 49%, about 44%, and about 43% hydrocodone bitartrate after 1 hr, respectively; about 60%, about 55%, and about 54% hydrocodone bitartrate after 2 hr, respectively; about 77%, about 72%, and about 71% hydrocodone bitartrate after 4 hr, respectively; about 89%, about 85%, about 84% hydrocodone bitartrate after 6 hr, respectively; about 97%, about 93%, and about 93% hydrocodone bitartrate after 8 hr, respectively; about 104%, about 100%, and about 102% hydrocodone bitartrate after 12 hr, respectively; and about 104%, about 102%, and about 105% hydrocodone bitartrate after 18 hr, respectively.

While the cumulative release profiles of the formulations generally decrease as the amount of the extended release component is increased, this trend is more pronounced for POLYOX® 1105 than for POLYOX® N-60K.

Example 30

In Vitro Dissolution of Controlled-Release Bilayer
Tablets Containing 15 mg Oxycodone and 650 mg
Acetaminophen Performed at a 150 rpm Paddle
Speed

Bilayer formulations described herein were prepared, each containing a total of 15 mg of oxycodone HCl and a total of 650 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the oxycodone HCl was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer.

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POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations were determined in a USP Type II apparatus. Six tablets were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and oxycodone from each batch are described in Table 75.

TABLE 75

Release rate data of bilayer tablets (15 mg oxycodone HCl; 325 mg acetaminophen) using a 150 rpm dissolution method.		
Time (hr)	Oxycodone HCl (%)	Acetaminophen (%)
0.25	33.7	54.4
0.50	39.0	56.5
1	47.4	60.6
2	61.4	68.1
4	81.7	81.1
6	95.2	90.8
8	101.2	96.0
12	102.3	97.6

Example 31

In Vitro Dissolution of Controlled-Release Bilayer Tablets Containing 15 mg Hydrocodone and 650 mg Acetaminophen Performed at a 150 rpm Paddle Speed

Bilayer formulations described herein were prepared, each containing a total of 15 mg of hydrocodone bitartrate and a total of 650 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the hydrocodone bitartrate was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® N60k was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations were determined in a USP Type II apparatus. Six tablets were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, and 18 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and hydrocodone bitartrate from each batch are described in Table 76.

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TABLE 76

Release rate data of bilayer tablets (15 mg hydrocodone bitartrate; 325 mg acetaminophen) using a 150 rpm dissolution method.				
Time (hr)	Hydrocodone Bitartrate		Acetaminophen	
	Mean (%)	RSD (%)	Mean (%)	RSD (%)
0.25	32.6	1.5	53.4	0.9
0.50	37.1	2.1	55.3	1.0
1	44.2	2.2	58.4	0.9
2	55.0	1.3	63.4	1.0
4	71.8	0.8	72.3	1.2
6	83.9	1.3	79.6	1.1
8	92.2	0.6	85.7	1.1
12	99.5	0.7	93.7	1.1
18	101.0	0.7	97.2	1.0

Example 32

Ethanol Release Testing at a 100 rpm Paddle Speed

The ethanol release studies discussed above in Example 8 were repeated, except that the solutions were stirred at a paddle speed of 100 rpm and additional aliquots were sampled at 240 min and 480 min. Tables 77, 78, 79, 80, and 81 present the percent release of OC and APAP in the presence of 0%, 5%, 10%, 20%, and 40% ethanol, respectively. FIG. 59 presents dissolution profiles for OC and FIG. 60 presents dissolution profiles for APAP in the presence of 0%, 5%, 20%, and 40% ethanol. Like the results at a paddle speed of 150 rpm, these data reveal that, for both OC and APAP, the dissolution in 5%, 20%, or 40% ethanol was either comparable or slower than the dissolution in 0% ethanol, indicating no dose dumping for this formulation.

TABLE 77

Percent Release in 0% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Minimum	Maximum	Mean	RSD	Minimum	Maximum
15	32.5	3.7	31.5	36.0	52.2	1.6	50.7	53.4
30	37.6	2.5	36.6	39.9	54.6	1.4	53.2	55.7
45	42.1	2.7	40.9	44.8	56.8	1.4	55.3	57.9
60	45.8	2.1	44.6	48.1	58.8	1.4	57.4	59.8
75	49.6	2.3	48.2	52.2	60.8	1.4	59.2	61.8
90	53.1	2.4	51.7	55.8	62.6	1.4	60.9	63.8
105	56.3	2.4	54.8	59.3	64.3	1.4	62.6	65.6
120	59.5	2.5	57.6	63.0	66.0	1.4	64.2	67.3
240	80.3	2.5	77.3	84.9	78.6	1.8	76.3	80.6
480	102.4	1.8	100.5	107.2	95.5	1.6	92.6	97.7

TABLE 78

Percent Release in 5% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Minimum	Maximum	Mean	RSD	Minimum	Maximum
15	31.5	2.5	30.0	32.9	52.6	2.1	51.4	55.1
30	36.8	2.4	35.6	38.5	55.1	2.0	53.8	57.6
45	40.9	2.8	38.9	43.5	57.1	2.0	55.8	59.6
60	44.6	3.7	42.1	48.4	58.9	2.0	57.6	61.4
75	48.0	3.6	46.0	52.6	60.7	1.9	59.4	63.2
90	51.0	3.1	49.3	55.3	62.3	1.9	61.0	64.7
105	54.3	3.2	51.8	58.6	63.9	2.0	62.6	66.4

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TABLE 78-continued

Percent Release in 5% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini-mum	Maxi-mum	Mean	RSD	Mini-mum	Maxi-mum
120	57.1	3.2	54.6	61.7	65.5	1.9	64.1	67.8
240	76.6	3.2	73.8	83.0	77.2	2.1	75.5	80.6
480	99.9	2.7	95.8	106.8	94.4	1.7	92.6	98.1

TABLE 79

Percent Release in 10% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini-mum	Maxi-mum	Mean	RSD	Mini-mum	Maxi-mum
15	30.3	3.1	28.9	32.1	51.7	1.8	50.1	53.4
30	35.6	3.3	33.7	37.3	54.1	1.9	52.4	55.8
45	39.6	2.6	37.6	40.9	56.0	1.9	54.3	57.8
60	43.1	2.6	41.2	44.7	57.8	1.9	56.1	59.5
75	46.2	2.3	44.1	47.5	59.5	1.8	57.7	61.1
90	49.3	2.1	47.3	50.6	61.1	1.8	59.3	62.8
105	52.2	2.2	50.1	53.6	62.6	1.8	60.9	64.2
120	54.8	2.3	52.8	56.4	64.1	1.8	62.3	65.6
240	73.8	2.2	70.8	76.1	75.5	1.7	73.4	77.4
480	98.4	2.1	94.7	101.1	93.5	1.6	91.0	95.9

TABLE 80

Percent Release in 20% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini-mum	Maxi-mum	Mean	RSD	Mini-mum	Maxi-mum
15	28.0	6.0	23.9	30.3	50.2	5.1	43.0	53.0
30	33.6	4.5	30.7	35.6	53.4	3.1	49.5	55.9
45	37.9	2.9	35.7	39.6	55.5	2.6	52.6	57.9
60	41.2	3.1	39.2	43.2	57.3	2.3	55.1	59.8
75	44.1	2.9	42.3	46.6	59.0	2.2	57.0	61.4
90	46.5	3.5	42.7	49.1	60.5	2.1	58.6	62.9
105	49.8	2.9	48.0	52.8	61.9	2.1	60.2	64.4
120	52.2	2.8	49.9	54.8	63.3	2.0	61.7	65.9
240	72.2	2.1	69.4	74.7	76.0	1.7	74.1	78.4
480	95.7	2.3	91.7	98.7	91.9	1.7	89.3	94.6

TABLE 81

Percent Release in 40% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini-mum	Maxi-mum	Mean	RSD	Mini-mum	Maxi-mum
15	11.9	13.9	10.0	15.1	16.7	23.2	12.3	22.9
30	21.1	15.4	17.3	26.2	30.4	22.3	21.7	40.7
45	26.8	11.6	22.4	30.3	38.5	15.3	29.6	44.8
60	30.8	7.0	26.8	34.0	43.1	9.2	35.9	47.1
75	34.2	5.0	31.5	36.8	46.1	5.3	41.1	49.2
90	36.9	3.2	35.1	38.8	48.3	3.3	44.6	50.2
105	39.6	3.3	37.3	41.2	49.8	2.4	47.3	51.3
120	41.9	3.3	39.4	44.2	51.1	2.3	48.3	52.7
240	57.0	1.8	55.7	58.9	60.8	2.0	58.9	63.6
480	80.6	1.6	78.4	83.7	77.2	1.3	75.7	78.7

All references cited herein are hereby incorporated by reference. The foregoing is offered primarily for purposes of

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illustration. It will be readily apparent to those skilled in the art that further drugs can be included, and that the shapes, components, additives, proportions, methods of formulation, and other parameters described herein can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed is:

1. An extended release pharmaceutical composition, comprising:

10 an immediate release portion comprising, by total weight of the immediate release portion, about 0.5% to about 2.5% of oxycodone or a pharmaceutically acceptable salt of oxycodone, and about 65% to about 85% of acetaminophen; and

15 an extended release portion comprising, by total weight of the extended release portion, about 0.3% to about 1.0% of oxycodone or a pharmaceutically acceptable salt of oxycodone and about 15% to about 25% of acetaminophen;

20 wherein the total amount of acetaminophen in the composition is about 200 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 5 mg to about 15 mg;

wherein when the composition is orally administered to a subject in need thereof the composition delivers the oxycodone or the pharmaceutically acceptable salt thereof and the acetaminophen to the subject's upper gastrointestinal tract for at least about 4 hours to about 12 hours; and

30 wherein either the oxycodone or the acetaminophen produces a plasma profile characterized by at least one pharmacokinetic parameter selected from the group consisting of C_{max} , C_{1hr} , C_{2h} , AUC, partial AUC, T_{max} and T_{lag} that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

35 2. The extended release pharmaceutical composition of claim 1, wherein the pharmacokinetic parameter selected from the group consisting of C_{max} , C_{1hr} , C_{2h} , AUC, partial AUC, T_{max} and T_{lag} differs by less than about 20%.

40 3. The extended release pharmaceutical composition of claim 1, wherein the pharmacokinetic parameter is selected from the group consisting of AUC and C_{max} .

4. The extended release pharmaceutical composition of claim 1, wherein both the oxycodone and the acetaminophen produce a plasma profile characterized by at least one pharmacokinetic parameter selected from the group consisting of C_{max} , C_{1hr} , C_{2h} , AUC, partial AUC, T_{max} and T_{lag} that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

50 5. The extended release pharmaceutical composition of claim 1, wherein the composition releases the oxycodone at a rate that is sufficient to delay gastric emptying but insufficient to cause an adverse gastrointestinal effect.

6. The extended release pharmaceutical composition of claim 1, wherein the extended release portion comprises at least one extended release polymer.

7. The extended release pharmaceutical composition of claim 6, wherein the at least one extended release polymer is a polyethylene oxide.

60 8. The extended release pharmaceutical composition of claim 7, wherein the polyethylene oxide has a molecular weight from about 500,000 Daltons to about 10,000,000 Daltons.

9. The extended release pharmaceutical composition of claim 6, wherein the at least one extended release polymer absorbs water and swells to a size sufficient for gastric retention.

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10. The extended release pharmaceutical composition of claim 1, wherein the total amount of the acetaminophen in the composition is about 325 mg; and the total amount of the oxycodone in the composition is about 7.5 mg.

11. The extended release pharmaceutical composition of claim 1, wherein the composition delivers the oxycodone or the pharmaceutically acceptable salt thereof and the acetaminophen to the subject's upper gastrointestinal tract for at least about 6 hours.

12. The extended release composition of claim 1, wherein the composition comprises (a) two immediate release portions in which one of the immediate release portions contains the oxycodone and the other immediate release portion contains the acetaminophen, and (b) two extended release portions in which one of the extended release portions contains the oxycodone and the other extended release portion contains the acetaminophen.

13. An extended release therapeutically effective pharmaceutical composition, comprising:

at least one immediate release portion comprising oxycodone or a pharmaceutically acceptable salt thereof and acetaminophen and at least one extended release portion comprising an extended release component, oxycodone or a pharmaceutically acceptable salt thereof, and acetaminophen;

wherein the at least one immediate release portion comprises from about 20% to about 30% (w/w) of the total amount of the oxycodone or a pharmaceutically acceptable salt thereof, and about 40% to about 60% (w/w) of the total amount of the acetaminophen in the composition;

wherein the at least one extended release portion comprises from about 70% to about 80% (w/w) of the total amount of the oxycodone or a pharmaceutically acceptable salt thereof, and about 40% to about 60% (w/w) of the total amount of the acetaminophen in the composition;

wherein the sum of the amounts of the acetaminophen in the immediate release and the extended release portions is about 325 mg;

wherein the sum of the amounts of the oxycodone or pharmaceutically acceptable salt thereof in the immediate release and extended release portions is about 7.5 mg; and

wherein the bioavailability of the acetaminophen and the oxycodone or the pharmaceutically acceptable salt thereof is not affected by the absence of food in a subject's gastrointestinal tract.

14. The extended release therapeutically effective pharmaceutical composition of claim 13, wherein when the pharmaceutical composition is administered to a subject under fasted conditions, mean AUC for oxycodone of the subject is about 9.0 ng-hr/mL/mg to about 18.5 ng-hr/mL/mg and the mean AUC for acetaminophen of the subject is about 35.0 ng-hr/mL/mg to about 80.0 ng-hr/mL/mg.

15. The extended release therapeutically effective pharmaceutical composition of claim 13, wherein the pharmaceutical composition is prepared using a process comprising dual granulation.

16. The extended release therapeutically effective pharmaceutical composition of claim 15, wherein the dual granulation comprises (a) granulating a first mixture comprising the oxycodone or a pharmaceutically acceptable salt thereof and at least one excipient to form a plurality of oxycodone-protected granules; and (b) granulating a second mixture comprising the plurality of oxycodone-protected granules, the acetaminophen, and at least one excipient to form a plurality of tablet granules.

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17. The extended release therapeutically effective pharmaceutical composition of claim 16, wherein the plurality of oxycodone-protected granules further comprises at least one excipient selected from the group consisting of a binder, a filler, an antioxidant, and a chelating agent.

18. The extended release therapeutically effective pharmaceutical composition of claim 13, wherein the composition has gastric retentive properties.

19. A method of treating acute pain in a patient in need thereof, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 13 to the patient.

20. The extended release pharmaceutical composition of claim 1, wherein the composition is gastric retentive.

21. A method of treating acute pain in a patient in need thereof, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 1 to the patient.

22. An extended release pharmaceutical composition, comprising:

an immediate release portion comprising about 20% to about 30% (w/w) of the total amount of the oxycodone or a pharmaceutically acceptable salt thereof in the composition, and about 40% to about 60% (w/w) of the total amount of the acetaminophen in the composition; and an extended release portion comprising about 70% to about 80% (w/w) of the total amount of the oxycodone or a pharmaceutically acceptable salt thereof in the composition, and about 40% to about 60% (w/w) of the total amount of the acetaminophen in the composition;

wherein the total amount of acetaminophen in the composition is about 200 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 5 mg to about 15 mg;

wherein when the composition is orally administered to a subject in need thereof the composition delivers the oxycodone or the pharmaceutically acceptable salt thereof and the acetaminophen to the subject's upper gastrointestinal tract for at least about 4 hours; and

wherein either the oxycodone or the acetaminophen produces a plasma profile characterized by at least one pharmacokinetic parameter selected from the group consisting of C_{max} , C_{1hr} , C_{2hr} , AUC, partial AUC, T_{max} , and T_{lag} that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

23. The extended release pharmaceutical composition of claim 22, wherein the composition is a bilayer tablet.

24. The extended release pharmaceutical composition of claim 22, wherein the composition comprises about 325 mg of acetaminophen and about 7.5 mg of oxycodone.

25. The extended release pharmaceutical composition of claim 22, wherein the composition further comprises at least one extended release polymer.

26. A method of treating acute pain in a patient in need thereof, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 22 to the patient.

27. The method of claim 26, wherein the composition is administered to the patient at 8-hour, 12-hour, or 24-hour dosing intervals.

28. The method of claim 26, wherein the composition is administered to the patient every 12 hours without regard to food.

29. A solid oral dosage form, comprising:

an immediate release portion comprising about 20% to about 30% (w/w) of the total amount of the oxycodone or a pharmaceutically acceptable salt thereof in the dos-

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age form, and about 40% to about 60% (w/w) of the total amount of the acetaminophen in the dosage form; and an extended release portion comprising about 70% to about 80% (w/w) of the total amount of the oxycodone or a pharmaceutically acceptable salt thereof in the dosage form, and about 40% to about 60% (w/w) of the total amount of the acetaminophen in the dosage form; wherein the total amount of oxycodone or salt in the dosage form is about 7.5 mg and the total amount of acetaminophen in the dosage form is about 325 mg; wherein the dosage form has gastric retentive properties; and wherein the bioavailability of either the acetaminophen or the oxycodone or the pharmaceutically acceptable salt thereof is not affected by the absence of food in a subject's gastrointestinal tract.

30. A method of treating acute pain in a patient in need thereof, comprising administering two solid dosage forms of claim 29 to the patient.

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EXHIBIT D

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(12) **United States Patent**
Park et al.

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(45) **Date of Patent:** ***Mar. 17, 2015**

(54) **METHODS OF PRODUCING STABILIZED
SOLID DOSAGE PHARMACEUTICAL
COMPOSITIONS CONTAINING
MORPHINANS**

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This patent is subject to a terminal dis-
claimer.

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2008/0026052 A1 * 1/2008 Schoenhard 424/456

FOREIGN PATENT DOCUMENTS

WO WO 2008015221 A2 * 2/2008

OTHER PUBLICATIONS

Michael J. Akers. Excipient—Drug Interactions in Parenteral For-
mulations. Journal of Pharmaceutical Sciences, vol. 91, No. 11, Nov.
2002, pp. 2283-2300.*

* cited by examiner

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(57) **ABSTRACT**

Methods for producing stabilized solid dosage form pharma-
ceutical compositions are provided. In particular, methods for
preparing protected granules containing morphinans, and
solid dosage form pharmaceutical compositions produced
using the morphinan-protected granules are provided.

30 Claims, No Drawings

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METHODS OF PRODUCING STABILIZED SOLID DOSAGE PHARMACEUTICAL COMPOSITIONS CONTAINING MORPHINANS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/166,770 filed on Jun. 22, 2011, which is a continuation-in-part of U.S. application Ser. No. 12/973,962, filed Dec. 21, 2010, which claims priority to U.S. Provisional Application No. 61/284,651 filed on Dec. 22, 2009, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to methods of producing stabilized solid dosage forms of morphinan pharmaceutical compositions. In particular, the present invention relates to methods of preparing morphinan-protected granules that may be incorporated into solid dosage forms of morphinan pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Minimizing the degradation of active pharmaceutical ingredients (APIs) in pharmaceutical compositions is an ongoing challenge in research and development. Degradation may occur from the physical or chemical instability of the API with incompatible pharmaceutical carriers in a pharmaceutical composition, or by reactions of the API with headspace oxygen or residual water in a composition.

Oxidation is a common mechanism of API degradation in pharmaceutical compositions. The process of oxidative degradation may occur via various mechanisms such as autooxidation, nucleophilic addition, electrophilic addition, or electron transfer. Regardless of the mechanism, degradant compounds formed by the degradation of an API in a pharmaceutical composition may impart potentially harmful properties to the composition.

If degradants are present in a pharmaceutical composition above the levels prescribed by ICH Guidelines Q3A and Q3B, the degradants must undergo a qualification procedure as part of the approval process required before the use and sale of the composition is allowed. Qualification of impurities typically involves costly studies using multiple animal models, and introduces considerable risk into the development process. If degradants of a pharmaceutical composition are found to be carcinogenic or teratogenic, the composition will not gain FDA approval, diminishing the opportunity for commercialization of the API.

As a result, the process of selecting functional carriers for a pharmaceutical composition is particularly challenging. A functional pharmaceutical carrier is typically selected primarily to impart desired performance characteristics to the composition such as an extended release profile. In addition, it is desirable to select functional carriers that are chemically compatible with the API in the composition. In certain compositions, it may be necessary to incorporate functional carriers that may be incompatible with the API in order to achieve a desired performance of the API in the body. In this situation, identifying an effective means to prevent the degradation of the API is an essential part of the development of a successful therapeutic composition.

For example, the formulation of a solid dosage form of an API may incorporate a release-modifying pharmaceutical

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carrier in order to achieve a desired release profile after administration of the compound. Polymer carriers such as a polyethylene oxide (PEO) polymer may be incorporated into a pharmaceutical composition to impart an extended release profile to the composition. PEO polymers are produced by a process of radical polymerization process followed by oxidative degradation of the polymer to achieve the desired molecular weight. The resulting PEO polymer carriers may retain residual peroxides and other oxidative species from the production process that may cause the oxidation of the API molecules in any pharmaceutical composition that incorporates PEO polymers. Typically, other excipients such as antioxidants or pH-lowering excipients may be incorporated into the API composition to minimize the degradation of the API in the presence of incompatible carriers such as PEO polymers in the pharmaceutical composition. However, in a solid dosage form composition, this approach is less effective than in other dosage forms such as solutions or suspensions.

Morphinans, a widespread class of analgesic APIs, are particularly vulnerable to oxidative degradation, especially in compositions that incorporate PEO polymer carriers or other pharmaceutical carriers that contain residual peroxides or other oxidative species. Because the physiological effects of morphinans are notoriously sensitive to small changes in chemical structure, the formation of degradants may introduce undesirable properties to a pharmaceutical composition in which a morphinan is vulnerable to degradation. For solid dosage forms of morphinan compositions, the introduction of additional antioxidant excipients or pH-lowering excipients to prevent the degradation of the morphinan, particularly when formulated in a solid dosage form, has been relatively ineffective to date.

A need exists in the art for a method of protecting an API from degradation in a solid dose form of a pharmaceutical composition. In particular, a need exists for a method of stabilizing morphinan APIs, which are especially vulnerable to oxidative degradation, in solid dosage forms of pharmaceutical compositions.

SUMMARY OF THE INVENTION

Briefly, therefore, one aspect of the disclosure provides a method for the preparation of a solid dosage form pharmaceutical composition comprising a morphinan and at least one other active pharmaceutical ingredient. The method comprises three steps. In the first step, a mixture comprising the morphinan and at least one excipient is granulated in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced thereby forming a morphinan-protected granule. The second step comprises granulating a mixture comprising the morphinan-protected granule, the active pharmaceutical agent, and at least one excipient to form a granulated mixture. In the third step, the granulated mixture is blended with a release-controlling polymer comprising a polyethylene oxide polymer to form the solid dosage form pharmaceutical composition comprising a sustained release layer.

In another aspect of the disclosure, a method for the preparation of a solid dosage form pharmaceutical composition comprising oxycodone and acetaminophen is provided. The method comprises three steps. In the first step, a mixture comprising the oxycodone and at least one excipient is granulated in a manner such that the amount of oxycodone exposed on the surface of the granule is substantially reduced thereby forming an oxycodone-protected granule. In the next step, a mixture comprising the oxycodone-protected granule, the acetaminophen, and at least one excipient is granulated to

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form a granulated mixture. The third step comprises blending the granulated mixture with a release-controlling polymer comprising a polyethylene oxide polymer is granulated to form the solid dosage form pharmaceutical composition comprising a sustained release layer.

An additional aspect of the disclosure provides a method for the preparation of a bilayer tablet comprising a sustained release layer and an immediate release layer. The method comprises four steps. In a first step, a mixture comprising oxycodone or hydrocodone and at least one excipient is granulated in a manner such that the amount of oxycodone or hydrocodone exposed on the surface of granule is substantially reduced thereby forming a morphinan-protected granule. In the next step, a mixture comprising the morphinan-protected granule, the acetaminophen, and at least one excipient is granulated to form a granulated mixture. In the third step, the granulated mixture is blended with a release-controlling polymer comprising a polyethylene oxide polymer to form a sustained release layer. In the final step, a mixture comprising the morphinan-protected granule from the first step is granulated with the acetaminophen and at least one excipient to form the immediate release layer.

A further aspect of the disclosure encompasses a granule that is substantially resistant to oxidative degradation of oxycodone. The granule comprises an interior region substantially comprising oxycodone that is surrounded by an exterior region substantially comprising at least one excipient. Moreover, the granule contains less than about 0.5% w/w of the total mass of oxycodone of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

Another aspect of the disclosure provides a granule substantially resistant to oxidative degradation of hydrocodone. The granule comprises an interior region substantially comprising hydrocodone that is surrounded by an exterior region substantially comprising at least one excipient, wherein the granule contains less than about 0.5% w/w of the total mass of hydrocodone of a degradant selected from hydrocodone-n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

Yet another aspect of the disclosure provides a granule substantially resistant to oxidative degradation of a morphinan, the granule prepared by a process comprising granulating a mixture comprising the morphinan and at least one excipient in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced thereby forming the morphinan-protected granule.

An additional aspect of the disclosure encompasses a pharmaceutical composition comprising a plurality of oxycodone-containing granules substantially resistant to oxidative degradation of oxycodone and at least one pharmaceutically acceptable carrier. The plurality of granules comprise an interior region substantially comprising oxycodone that is surrounded by an exterior region substantially comprising at least one excipient, wherein the granule contains less than about 0.5% w/w of the total mass of oxycodone of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

Another aspect of the disclosure provides a pharmaceutical composition comprising a plurality of hydrocodone-containing granules substantially resistant to oxidative degradation of hydrocodone and at least one pharmaceutically acceptable carrier. The plurality of granules comprise an interior region substantially comprising hydrocodone that is surrounded by an exterior region substantially comprising at least one

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excipient, wherein the granule contains less than about 0.5% w/w of the total mass of hydrocodone of a degradant selected from hydrocodone n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

Yet another aspect provides a solid dosage pharmaceutical composition comprising a plurality of oxycodone-protected granules and acetaminophen, the composition prepared by a process comprising (a) granulating a mixture comprising the oxycodone and at least one excipient in a manner such that the amount of oxycodone exposed on the surface of the granule is substantially reduced thereby forming the plurality of oxycodone-protected granules; (b) granulating a mixture comprising the plurality of oxycodone-protected granules, the acetaminophen, and at least one excipient to form a granulated mixture; and (c) blending the granulated mixture with a release-controlling polymer comprising a polyethylene oxide polymer to form the solid dosage form the pharmaceutical composition comprising a sustained release layer.

Other features and iterations of the invention are described in more detail below.

DETAILED DESCRIPTION

The invention provides methods of preparing morphinan-protected granules by combining a morphinan with at least one excipient to form a mixture, and granulating the mixture. The resulting morphinan-protected granules have a physical structure that minimizes the amount of morphinan that is exposed on the surface of the granule. The morphinan-protected granules may stabilize the morphinan against various mechanisms of degradation such as oxidation by substantially decreasing the amount of morphinan exposed on the surface of the granule thereby reducing the degree of contact between the morphinan and the oxidative species in the environment surrounding the granules, including but not limited to carriers and residual water in the composition, and atmospheric oxygen and moisture.

In addition, if chemically protective excipients including but not limited to antioxidants and pH-adjusting agents are included in the excipient mixture forming the morphinan-protected granule, the morphinan contained within the granule is further protected against degradation. Any oxidative species contained in the environment surrounding the morphinan-protected granules may react with the chemically protective excipients situated the granules before they can reach the morphinan.

The morphinan-protected granules may be prepared using any device known in the art, including but not limited to a high-shear wet granulator. The particular device used for granulation may affect the physical properties of the resulting granules, including but not limited to granule size, granule density, and granule porosity, all of which may influence the protective properties of the granule against degradation of the morphinan. Regardless of the granulation method used to form the granules, the distribution of morphinan and excipients within the granules is influenced by at least several factors including but not limited to the size of the morphinan particles relative to the excipient particles in the mixture prior to granulation, the chemical properties of the morphinan and excipients including but not limited to hydrophobicity and ionic charge, and the presence of excipients dissolved in the granulation solution used to prepare the granules.

The morphinan-protected granules prepared by the methods of the invention may be incorporated into a solid dose form of a pharmaceutical composition, including but not limited to tablet and capsule formulations. In addition to protec-

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tion against degradation, the inclusion of the morphinan in the form of granules imparts several other advantageous aspects to the resulting composition. Because the morphinan in the granules is protected, the choice of carrier may be selected to satisfy constraints other than compatibility with the morphinan. Carriers in the composition may instead be selected based on factors including but not limited to the cost of the carrier, the desirable modified-release properties imparted by a particular carrier. Further, variation in the characteristics of the morphinan-protected granules including granule size, excipients included in the granules, and the physical structure of the granules may be used to control the release profile or other pharmacokinetic characteristics of pharmaceutical compositions.

Detailed descriptions of various embodiments of the morphinan protected granules, methods of preparing the morphinan protected granules, and solid dosage forms of pharmaceutical compositions that include the morphinan-protected granules are described in detail below.

(I) Morphinan-Protected Granules

The granules prepared by the methods of the invention stabilize the morphinan contained within the granules by substantially reducing the amount of morphinan exposed on the surface of the granule. In this regard, significantly less of the morphinan is in contact with any oxidative species in the environment outside of the granule, and may additionally provide chemical protection of the morphinan against degradation by surrounding the morphinan with chemically protective excipients including but not limited to antioxidants that are contained within the morphinan-protected granule. The physical structure of the morphinan-protected granule may influence the protective efficacy of the granule against degradation of the morphinan, and further influences the suitability of the granules for inclusion in various solid dose forms of pharmaceutical compositions, including but not limited to tablets and capsules.

(a) Granule Structure

The physical structure of the granule includes the morphinan dispersed within the excipient mixture and granulated in a manner such that the amount of morphinan exposed on the surface of the granule is substantially reduced. The particular physical structure of any embodiment of a morphinan-protected granule is influenced by at least several factors related to the method of preparing the granules and the particular morphinan and excipients included in the granule. The influence of these factors on the physical structure of the granules is described in detail below.

In general, the physical structure of the granules may vary from an essentially random spatial distribution of the morphinan and excipients throughout the granules to a highly ordered distribution in which essentially all of the morphinan is contained within a sharply delineated interior region that is surrounded by an exterior region that contains essentially all of the excipients. In an embodiment, the amount of morphinan that is exposed at the surface of the granules is less than about 100% of the total weight of the morphinan in the granules. In other embodiments, the amount of morphinan that is exposed at the surface of the granules is less than about 95%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, and less than about 5% of the total weight of morphinan in the granule.

Excipients contained within the granule may provide additional protection against degradation of the morphinan by

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chemically interacting with degradative compounds surrounding or within the granule. For example, the effectiveness of the excipients at protecting the morphinans in the granule may be enhanced if at least one of the excipients includes but is not limited to an antioxidant, a chelating agent, or a pH-adjusting agent. Various embodiments of the excipients included in the granule are described in detail below.

The density and porosity of the exterior regions of the granules may influence the effectiveness of the exterior regions at protecting the morphinans in the granules from degradation. Exterior regions having higher densities and lower porosities may be more resistant to penetration by degradative compounds from outside the granule. The densities and porosities of the exterior regions of the granules may be influenced by at least several factors including but not limited to the particular morphinan and excipients included in the granule and the device used to prepare the granule. For example, a granule prepared using a high-shear wet granulator may have a higher density and lower porosity compared to a granule with a similar composition prepared using a fluid bed granulator.

The d_{90} of the granules in various embodiments may be selected based on the intended use of the granules, in particular the particular solid dosage form in which the granules are to be incorporated. The particular d_{90} of the granule may be influenced by a variety of factors including but not limited to the composition of the granule and the granulation device used to prepare the granules. The d_{90} of the granules may be larger for granule compositions having a higher proportion of excipients including but not limited to binders and fillers relative to other types of excipients.

In various embodiments, the granules may have an average d_{90} of less than about 2000 μm . In other embodiments, the granules may have an average d_{90} of less than about 1800 μm , less than about 1500 μm , less than about 1000 μm , less than about 900 μm , less than about 800 μm , less than about 700 μm , less than about 600 μm , less than about 500 μm , less than about 400 μm , less than about 300 μm , less than about 200 μm , less than about 150 μm , and less than about 100 μm . In one exemplary embodiment in which the granules are to be incorporated in a solid dosage form including but not limited to a capsule, the granules may be less than about 1000 μm in average d_{90} . In another exemplary embodiment in which the granules are to be incorporated in a solid dosage form including but not limited to a tablet, the granules may be less than about 800 μm in average d_{90} . In yet another embodiment, the granules may range from about 150 μm to about 200 μm in average d_{90} .

(II) Granule Composition

The composition of the granules prepared using the methods of the invention include a morphinan and at least one excipient. The particular composition of the granules may influence a variety of properties of the granules including but not limited to the physical structure of the granules, the stability of the morphinan contained within the granule, and the suitability of the granules for incorporation into a particular dry dosage form of a pharmaceutical composition.

One aspect of the composition that may influence the physical structure of the granules is the d_{90} of the morphinan particles relative to the d_{90} of the excipient particles in the mixture that used to form the granules. As used herein, d_{90} represents the particle diameter at which 90% of the individual particles of a compound are smaller than the specified diameter. Without being bound to any particular theory, when a granulation device including but not limited to a low-shear

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wet granulator, a high-shear wet granulator, or a fluid bed granulator is used to granulate the mixture of the morphinan and at least one excipient, the compounds having a smaller d_{90} relative to the other compounds in the mixture tend to aggregate near the interior regions of the granules, and the compounds having larger d_{90} tend to aggregate near the exterior regions of the granules, regardless of whether the compound is a morphinan or an excipient.

As a practitioner skilled in the art may appreciate, for granule compositions in which the morphinan accounts for an extremely low proportion of the total mass of the granule, the size of the morphinan particles relative to the excipient particles may not exert the same influence on the physical structure of the resulting granules as described previously. By way of a non-limiting example, if a granule is prepared using a mixture containing about 5% morphinan and about 95% excipients by weight, and the d_{90} of the morphinan is larger than the d_{90} of the excipients, the relative scarcity of the morphinan particles may result in a granule in which the individual morphinan particles are surrounded by excipient particles, and the morphinan particles may be located in both the interior region and the exterior region of the granule.

In one embodiment, the d_{90} of the morphinan is smaller than the d_{90} of the excipients. In another embodiment, the d_{90} of the morphinan is less than about 80% of the d_{90} of the excipients. In yet other embodiments, the d_{90} of the morphinan is less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, or less than about 50% of the d_{90} of the excipients.

The d_{90} values of the morphinan and the excipients may also be influenced by the capabilities of the particular device used to prepare the granules. Without being bound to any particular theory, when a granulation device including but not limited to a low-shear wet granulator, a high-shear wet granulator, or a fluid bed granulator is used to granulate the mixture of the morphinan and at least one excipient, if the d_{90} of a particular compound falls below a threshold d_{90} , the particles of that compound tend to aggregate before they are granulated, resulting in granules that have a non-homogenous distribution of the compound from granule to granule.

In other embodiments, other properties of the morphinan and excipients may influence the physical structure of the granule including but not limited to the hydrophobicity and ionic charge of the morphinan relative to the one or more excipients. As a non-limiting illustrative example, if the morphinan is hydrophobic relative to the excipients and if a polar granulation fluid is used in the granulation process, hydrophobic repulsive forces may tend to situate the morphinan within the interior region of the granules.

In one embodiment, the composition of the granules includes one morphinan compound. In other embodiments, the composition of the granules may further include one or more additional morphinan compounds within each granule. Any number of different morphinans may be included in the composition of the granules, so long as all morphinans that are included in the granule are physically and chemically compatible.

An acid, as defined herein, refers to the acid and any pharmaceutically acceptable salt of the acid.

(a) Morphinans

The compositions of various embodiments of the granules include a morphinan. In one embodiment, the morphinan may be included in the granules in an amount of up to about 90% of the total weight of the granules. In other embodiments, the morphinan may be included in the granules in an amount ranging up to about 80%, up to about 70%, up to about 60%, up to about 50%, up to about 40%, up to about 30%, up to about 20%, up to about 10%, up to about 1%, and up to about 0.5% of the total weight of the granules.

The morphinan included in various embodiments of the granules may be selected from opium, natural opium deriva-

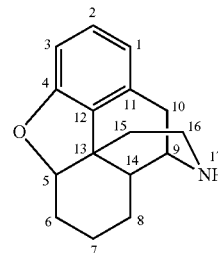
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tives, semi-synthetic opium derivatives, and synthetic opium derivatives. Non-limiting examples of suitable morphinans for various embodiments of the granules include adlumine, allocryptopine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bulbocapnine, buprenorphine, butorphanol, canadine, capaurine, chelerythrine, chelidonine, codamine, codeine, coptisine, coreximine, corlumine, corybulbine, corycavamine, corycavine, corydaline, corydine, corytuberine, cularine, cotamine, cryptopine, cycloartenol, cycloartenone, cyclolaudenol, dehydroreticuline, desomorphine, dextropropoxyphene, dextrorphanol, diacetylmorphine, dicentrine, dihydrosanguinarine, dipropanoylmorphine, epiporphyroxine, ethylmorphine, eupaverine, fagarine, fentanyl, glaucine, homochelidonine, hydrocodone, hydrocotamine, hydromorphone, hydroxythebaine, isoboldine, isocorybulbine, isocorydine, isocorypalmine, isoquinoline, laudanidine, laudanine, laudanone, levorphanol, magnoflorine, meconic acid, methadone, morphine, nalbuphine, nalmeferine, naloxone, naltrexamine, α -naltrexol, β -naltrexol, naltrexone, naphthaphenanthridine, narceine, narceinone, narcotoline, narcotine, neopine, nicomorphine, norlaudanone, norsanguinarine, noscapine, opium, oripavine, oxycodone, oxymorphone, oxysanguinarine, palaudine, papaverine, papaveraldine, papaverrubine, perparin, pethidine, phenanthrene, phtalide-isoquinoline, porphyroxine, protopine, pseudocodeine, pseudomorphine, reticuline, salutaridine, sinoacutine, sanguinarine, scoulerine, somniferine, stepholidine, tapentadol, tetrahydroprotoberberine, thebaine, tramadol, and xanthaline. In an exemplary embodiment, the morphinan included in the granules may be selected from oxycodone, oxymorphone, hydrocodone, hydromorphone, nalbuphine, naloxone, buprenorphine, and naltrexone. In another exemplary embodiment, the morphinan in the granules is oxycodone or hydrocodone.

Any of the morphinans included in the embodiments of the granules may have a (-) or (+) orientation with respect to the rotation of polarized light, depending upon whether the starting substrate has (-) or (+) optical activity, and are referred to herein as (-)-morphinans and (+)-morphinans respectively. More specifically, each chiral center may independently have an R or an S configuration.

As an illustrative example, an embodiment of the granules may include a morphinan compound possessing a fused carbon ring structure. The ring atoms of the morphinan compound may be numbered as diagrammed in Formula (I) below. Morphinan compounds have asymmetric centers and the core morphinan compound may have at least four chiral carbons including but not limited to C-5, C-13, C-14, and C-9. In various embodiments, the configuration of the chiral carbons C-5, C-13, C-14, and C-9 may be RRRR, RRSR, RRRS, RRSS, RSRR, RSSR, RSRS, RSSS, SRRR, SRSR, SRRS, SSRR, SSSR, SSRS, or SSSS, provided that the C-15 and the C-16 carbons are both oriented either on the alpha face or the beta face of the morphinan molecule.

(I)



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In various embodiments of the granules, the morphinan may be provided in any solid form including but not limited to a finely divided solid, a crystal, a particle, a powder, or any other finely divided solid form known in the art. Any finely divided solid form of the morphinan may be used so long as the d_{90} of the morphinan particles are smaller than the d_{90} of the one or more excipients as described above.

(b) Excipients

Various embodiments of the granules include one or more excipients in addition to the morphinan. In general, the one or more excipients are selected to impart at least one or more desired physical or chemical properties to the granules, including but not limited to adhesion of the particles of the morphinan and excipient compounds in the mixture to facilitate the formation of granules, formation of physical barriers around the morphinans in the granules, and chemical inhibition of various mechanisms of degradation of the morphinans including but not limited to oxidation. Non-limiting examples of the one or more excipients include binders, fillers, antioxidants, pH-adjusting agents, chelating agents, and antimicrobial agents.

In one embodiment, the one or more excipients may be introduced into the mixture to be granulated in a solid form including but not limited to a crystal, a particle, a powder, or any other finely divided solid form known in the art. In another embodiment, the one or more excipients may be dissolved or suspended in a solvent and sprayed onto the mixture in a granulation device as a binder fluid during granulation.

(i) Binders

In general, binders are excipients included in various embodiments of the granule to impart structural integrity to the granules by binding together the particles making up each granule. Non-limiting examples of binders suitable for the formulations of various embodiments include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof. The polypeptides may be any arrangement of amino acids ranging from about 100 to about 300,000 Daltons.

In one embodiment, the binder may be introduced into the mixture to be granulated in a solid form including but not limited to a crystal, a particle, a powder, or any other finely divided solid form known in the art. In another embodiment, the binder may be dissolved or suspended in a solvent and sprayed onto the mixture in a granulation device as a binder fluid during granulation.

(ii) Fillers

Fillers may be included in various embodiments of the granule composition as an excipient to increase the bulk volume of the granules and to impart suitable compressibility characteristics to the granules for subsequent inclusion in solid dosage forms of pharmaceutical compositions including but not limited to tablets. Non-limiting examples of fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. Other non-limiting examples of fillers include dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol.

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(iii) Antioxidants

Antioxidants are excipients included in various embodiments of the granules to prevent the oxidation of the morphinan in the granules. Suitable antioxidants include, but are not limited to anoxomer, N-acetylcysteine, benzyl isothiocyanate, m-aminobenzoic acid, o-aminobenzoic acid, p-aminobenzoic acid (PABA), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), caffeic acid, canthaxanthin, alpha-carotene, beta-carotene, beta-carotene, beta-apo-carotenoid acid, carnosol, carvacrol, catechins, chlorogenic acid, citric acid and its salts, clove extract, coffee bean extract, p-coumaric acid, 3,4-dihydroxybenzoic acid, N,N'-diphenyl-p-phenylenediamine (DPPD), dilauryl thiodipropionate, distearyl thiodipropionate, 2,6-di-tert-butylphenol, edetic acid, ellagic acid, erythorbic acid, sodium erythorbate, esculetin, esculin, 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline, ethyl maltol, ethylenediaminetetraacetic acid (EDTA) and EDTA salts, eucalyptus extract, eugenol, ferulic acid, flavonoids (e.g., catechin, epicatechin, epigallocatechin (EGC), flavones (e.g., apigenin, chrysin, luteolin), flavonols (e.g., datiscetin, myricetin, daemfero), flavanones, fraxetin, fumaric acid, gallic acid, gentian extract, gluconic acid, glycine, gum guaiacum, hesperetin, alpha-hydroxybenzyl phosphinic acid, hydroxycinnamic acid, hydroxyglutaric acid, hydroquinone, N-hydroxysuccinic acid, hydroxytyrosol, hydroxyurea, rice bran extract, lactic acid and its salts, lecithin, lecithin citrate; R-alpha-lipoic acid, lutein, lycopene, malic acid, maltol, 5-methoxy tryptamine, monoglyceride citrate; monoisopropyl citrate; morin, beta-naphthoflavone, nordihydroguaiaretic acid (NDGA), oxalic acid, palmityl citrate, phenothiazine, phosphatidylcholine, phosphoric acid, phosphates, phytic acid, phytalubichromel, pimento extract, polyphosphates, quercetin, trans-resveratrol, rosemary extract, rosmarinic acid, sage extract, sesamol, silymarin, sinapic acid, succinic acid, stearyl citrate, syringic acid, tartaric acid, thymol, tocopherols (i.e., alpha-, beta-, gamma- and delta-tocopherol), tocotrienols (i.e., alpha-, beta-, gamma- and delta-tocotrienols), tyrosol, vanilic acid, 2,6-di-tert-butyl-4-hydroxymethylphenol (i.e., Ionox 100), 2,4-(tris-3',5'-bi-tert-butyl-4'-hydroxybenzyl)-mesitylene (i.e., Ionox 330), 2,4,5-trihydroxybutyrophenone, ubiquinone, tertiary butyl hydroquinone (TBHQ), thiodipropionic acid, trihydroxy butyrophenone, tryptamine, tyramine, uric acid, vitamin K and derivatives, vitamin Q10, wheat germ oil, zeaxanthin, or combinations thereof.

In another embodiment, an antioxidant agent may be subjected to a particle size reduction process including but not limited to grinding, milling, sonication, or hammer milling in order to reduce the d_{90} of the antioxidant agent to a value less than the d_{90} of the morphinan (or other API included in the formulation) prior to granulation. In this embodiment, the reduced d_{90} of the antioxidant agent may result in a distribution of antioxidant agent that is clustered around the morphinan particles, rather than near the outer surface of the granule. A granule having this physical structure may provide comparable protection of the morphinan in the granules against degradation as compared to granules in which the antioxidant agent is situated on the outside of the granule using a significantly lower amount of the antioxidant agent.

In an exemplary embodiment, the granule composition includes at least one antioxidant including but not limited to citric acid and Na_2EDTA .

(iv) pH-Adjusting Agents

In various embodiments of the granule composition, a pH-adjusting agent may be included as an excipient to raise or lower the pH of the granule in order to prevent the oxidation of the morphinan in the granules. For example, a pH-adjust-

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ing agent including but not limited to citric acid may be incorporated into the composition granule in order to lower the pH of the granule. In this example, a lower pH prevents the oxidation of the granule by various oxidative compounds associated with release-modifying polymer incorporated into a solid dosage form, including but not limited to peroxides.

In another embodiment, a pH-adjusting agent may be subjected to a particle size reduction process including but not limited to grinding, milling, sonication, or hammer milling in order to reduce the d_{90} of the pH-adjusting agent to a value less than the d_{90} of the morphinan prior to granulation. In this embodiment, the reduced d_{90} of the pH-adjusting agent may result in a distribution of pH-adjusting agent that is clustered around the morphinan particles, rather than near the outer surface of the granule. Non-limiting examples of pH-adjusting agents include citric acid, acetic acid, tartaric acid, malic acid, fumaric acid, lactic acid, phosphoric acid, sorbic acid, benzoic acid, sodium carbonate and sodium bicarbonate.

(v) Chelating Agents

In various embodiments of the granule composition, a chelating agent may be included as an excipient to immobilize oxidative species including but not limited to metal ions in order to inhibit the oxidative degradation of the morphinan by these oxidative species. Non-limiting examples of chelating agents include lysine, methionine, glycine, gluconate, polysaccharides, glutamate, aspartate, and Na_2EDTA .

(vi) Antimicrobial Agents

In various embodiments of the granule composition, an antimicrobial agent may be included as an excipient to minimize the degradation of the morphinan by microbial agents including but not limited to bacteria and fungi. Non-limiting examples of antimicrobials include parabens, chlorobutanol, phenol, calcium propionate, sodium nitrate, sodium nitrite, Na_2EDTA and sulfites including but not limited to sulfur dioxide, sodium bisulfite, and potassium hydrogen sulfite.

(III) Granule Stability

In various embodiments of the granule composition, the morphinan in the granule is substantially resistant to degradation due to interactions of the morphinan with degradative compounds or conditions present in the environment or in the carriers surrounding the granules in a solid dosage form of a pharmaceutical composition. In one embodiment, the morphinan in the granules is substantially resistant to the formation of degradants resulting from a chemical change in the morphinan brought about during the production and/or storage of the pharmaceutical composition containing the morphinan by the effect of factors including but not limited to light, temperature, pH, water, or reaction with an excipient or carrier included in the pharmaceutical composition. The particular degradants formed in a pharmaceutical composition depend on the particular morphinan and the at least one excipient within the granule, as well as the particular carriers included in the pharmaceutical composition along with the granules.

Statutory requirements, including but not limited to ICH Guidelines Q3A and Q3B identify maximum allowable amounts of degradants above which the degradants must be reported and subjected to the qualification process described above. According to ICH Guideline Q3B, the amount of any individual degradant must be reported if the amount of degradant exceeds 0.10% of the total API weight for maximum daily doses of 1000 mg of API or below. For APIs having average daily doses of above 1000 mg, degradants in

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excess of 0.05% of the total API mass must be reported. The ICH guidelines apply throughout the effective shelf life of the pharmaceutical composition.

Although no standardized method of assessing API stability exists at present, drug developers typically subject potential pharmaceutical compounds to periods of storage at accelerated degradation conditions, typically defined as a temperature of about 40° C. and a relative humidity of about 75%. The period of storage time at the accelerated degradation conditions may vary from about 1 day to about 6 months, but is typically about 6 months. In an embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than 0.05%, less than 0.04%, less than 0.03%, less than 0.02%, or less than 0.01% of the total mass of the morphinan after about two months of storage at a temperature of about 40° C. and a relative humidity of about 75%. In another embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than 0.05%, less than 0.04%, less than 0.03%, less than 0.02%, or less than 0.01% of the total mass of the morphinan after about six months of storage at a temperature of about 40° C. and a relative humidity of about 75%. In yet another embodiment, the formation of any one degradant in the composition may be limited to less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.1%, less than 0.05%, less than 0.04%, less than 0.03%, less than 0.02%, or less than 0.01% of the total mass of the morphinan after about four weeks of storage at accelerated stability conditions at a temperature of about 40° C. and a relative humidity of about 75%.

In an exemplary embodiment, for a pharmaceutical composition incorporating oxycodone as the morphinan and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of oxycodone of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity. In another exemplary embodiment, for a pharmaceutical composition incorporating oxycodone and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of oxycodone of each of one or more degradants selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

In another exemplary embodiment, for a pharmaceutical composition incorporating hydrocodone as the morphinan and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of hydrocodone of a degradant selected from hydrocodone n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity. In another exemplary embodiment, for a pharmaceutical composition incorporating hydrocodone and at least one excipient in the form of granules, the granules contain less than about 0.5% w/w of the total mass of hydrocodone of each of one or more degradants selected from hydrocodone n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

(IV) Method of Preparing Granules

In various embodiments, the granules may be prepared by combining the morphinan with at least one excipient to form a mixture and granulating the mixture in a manner such that

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the amount of morphinan exposed on the surface of the granules is minimized (thereby forming a morphinan-protected granule).

Suitable morphinans for the granule embodiments are described in detail in Section (IIa) above, and suitable excipients are described in Section (IIb) above. The mixture may be formed using any suitable method known in the art including but not limited to stirring, shaking, vibrating, and blending. In an embodiment, the morphinan and dry excipients may be charged into a granulation device and mixed prior to the addition of the granulation fluid.

Any suitable granulation device known in the art may be used to prepare the granules. As previously discussed, the particular granulation device selected for the preparation of the granules may influence the physical properties of the resulting granules. Non-limiting examples of suitable devices for the preparation of the granules include a low-shear wet granulator, a high-shear wet granulator, a fluid-bed granulator, a roller compactor, a vertical granulator, an oscillating granulator, a gelatinizer, a pelletizer, and a spheronizer. The granulation device may be selected in order to prepare granules having the desired granule physical characteristics described in Section (II) above.

In an exemplary embodiment, a high-shear wet granulator is used to prepare the granules. The high-shear wet granulator may be capable of preparing granules having properties that enhance the protective effect of the granule, including but not limited to higher granule densities and lower granule porosities relative to granules prepared by other devices. Further, the high-shear wet granulator is capable of preparing granules with a d_{90} that is larger than other granulation devices, resulting in granules suitable for inclusion in a wider variety of solid dosage forms of morphinan compositions.

In the same exemplary embodiment, the morphinan and the excipients in dry form of the composition are introduced into the wet high shear granulator in order to form the mixture. After the morphinan and the dry excipients are essentially homogeneously distributed within the granulator, a granulation fluid is sprayed into the granulator. In various embodiments, the granulation fluid may be any volatile, non-toxic granulation fluid known in the art. Non-limiting examples of suitable granulation fluids include water, ethanol, isopropanol, and combinations thereof. In other embodiments, one or more of the excipients may be mixed with the granulation fluid prior to spraying the granulation fluid into the granulator. In an exemplary embodiment, a binder including but not limited to pregelatinized starch may be dissolved into the granulation fluid including but not limited to water to form a granulation solution, and the granulation solution may be sprayed into the granulator in order to prepare the granules.

In an additional embodiment, the wet granules prepared in the high shear wet granulator may be dried using a drying device, resulting in dried granules having a water content of less than about 5%, less than about 4%, less than about 3%, or less than about 2% of the total weight of the granules. Any suitable drying device known in the art may be used to dry the wet granules, including but not limited to an oven, a vacuum oven, and a rotary drum dryer.

(V) Solid Dosage Forms Incorporating Granules

The morphinan-protected granules prepared by various embodiments may be incorporated into various solid dosage pharmaceutical compositions. Non-limiting examples of solid dosage pharmaceutical compositions incorporating embodiments of the morphinan granules include granules, tablets, and capsules. Non-limiting embodiments of tablets

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include uncoated tablets, coated tablets, mini-tablets, orally disintegrating tablets, and bilayer tablets. Non-limiting embodiments of capsules include hard capsules and multi-layer capsules. Depending on the selection of particular formulation, the solid dosage pharmaceutical composition may have release characteristics including but not limited to rapid release, sustained release, extended release, slow release, time release, and combinations thereof.

In an exemplary embodiment, solid dosage form pharmaceutical compositions are made via a two step process. First, the morphinan-protected granule is formed. The morphinan-protected granule is then mixed with excipients and other active pharmaceutical ingredients, which are then granulated to form the solid dosage form pharmaceutical composition. The solid dosage form pharmaceutical composition may include additional APIs. In an exemplary embodiment, the solid dosage form pharmaceutical composition comprises a morphinan and acetaminophen. In additional embodiments, the solid dosage form pharmaceutical composition may comprise sustained release (SR) and immediate release layers (IR). Typically, the SR and IR layers both include the morphinan and acetaminophen. In each of the foregoing embodiments, the SR layer typically comprises a release-controlling polymer comprising a polyethylene oxide polymer.

(a) Compositions of Solid Dosage Forms

Various embodiments of the solid dosage pharmaceutical compositions incorporating the morphinan-protected granules may include one or more pharmaceutically acceptable carriers in addition to the granules. Pharmaceutically acceptable carriers suitable for embodiments of the solid dosage pharmaceutical compositions may include but are not limited to binders, fillers, lubricants, diluents, non-effervescent disintegrants, effervescent disintegrants, flavor-modifying agents, sweeteners, dispersants, coloring agents, taste masking agents, release-controlling polymers and combinations thereof.

(i) Binders

Non-limiting examples of binders suitable for the formulations of various embodiments include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof. The polypeptide may be any arrangement of amino acids ranging from about 100 to about 300,000 Daltons.

(ii) Fillers

Non-limiting examples of fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. Other non-limiting examples of fillers include dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol.

(iii) Lubricants

Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and light mineral oil.

(iv) Diluents

Diluents suitable for use include but are not limited to pharmaceutically acceptable saccharides such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol,

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tol, and sorbitol; polyhydric alcohols; starches; pre-manufactured direct compression diluents; and mixtures of any of the foregoing.

(v) Non-Effervescent and Effervescent Disintegrants

Non-limiting examples of non-effervescent disintegrants include starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, and tragacanth. Suitable effervescent disintegrants include but are not limited to sodium bicarbonate in combination with citric acid, and sodium bicarbonate in combination with tartaric acid.

(vi) Flavor-Modifying Agents

Suitable flavor-modifying agents include but are not limited to synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits, and combinations thereof. Other non-limiting examples of flavor-modifying agents include cinnamon oils, oil of wintergreen, peppermint oils, clover oil, hay oil, anise oil, eucalyptus, vanilla, citrus oils such as lemon oil, orange oil, grape and grapefruit oil, fruit essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, and apricot.

(vii) Sweeteners

Non-limiting examples of sweeteners include glucose (corn syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; *Stevia rebaudiana* (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1,2,3-oxathiazin-4-one-2, 2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof

(viii) Dispersants

Dispersants may include but are not limited to starch, alginic acid, polyvinylpyrrolidones, guar gum, kaolin, bentonite, purified wood cellulose, sodium starch glycolate, isoamorphous silicate, and microcrystalline cellulose as high HLB emulsifier surfactants.

(ix) Coloring Agents

Suitable coloring agents include but are not limited to food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors or dyes, along with their corresponding lakes, and certain natural and derived colorants may be suitable for use in various embodiments.

(x) Taste-Masking Agents

Taste-masking agents include but are not limited to cellulose hydroxypropyl ethers (HPC) such as Klucel®, Nisswo HPC and PrimaFlo HP22; low-substituted hydroxypropyl ethers (L-HPC); cellulose hydroxypropyl methyl ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Opadry YS, PrimaFlo, MP3295A, Benecel MP824, and Benecel MP843; methylcellulose polymers such as Methocel® and Metolose®; Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease; Polyvinyl alcohol (PVA) such as Opadry AMB; hydroxyethylcelluloses such as Natrosol®; carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aualon®-CMC; polyvinyl alcohol and polyethylene glycol copolymers such as Kollicoat IR®; monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® RD100, and Eudragit® E100; cellulose acetate phthalate; sepiifilms such

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as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials. In other embodiments, additional taste-masking agents contemplated are those described in U.S. Pat. Nos. 4,851,226, 5,075,114, and 5,876,759, each of which is hereby incorporated by reference in its entirety.

(xi) Release-Controlling Polymers

Release-controlling polymers may be included in the various embodiments of the solid dosage pharmaceutical compositions incorporating the granules. In one embodiment, the release-controlling polymers may be used as a tablet coating. In other embodiments, including but not limited to bilayer tablets, a release-controlling polymer may be mixed with the granules and other excipients prior to the formation of a tablet by a known process including but not limited to compression in a tablet mold. Suitable release-controlling polymers include but are not limited to hydrophilic polymers and hydrophobic polymers.

Suitable hydrophilic polymers include, but are not limited to, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose ethers, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, nitrocellulose, crosslinked starch, agar, casein, chitin, collagen, gelatin, maltose, mannitol, maltodextrin, pectin, pullulan, sorbitol, xylitol, polysaccharides, ammonia alginate, sodium alginate, calcium alginate, potassium alginate, propylene glycol alginate, alginate sodium carmellose, calcium carmellose, carrageenan, fucoidan, furcellaran, arabic gum, carrageens gum, ghattigum, guar gum, karayagum, locust beangum, okragum, tragacanth gum, scleroglucangum, xanthangum, hypnea, laminaran, acrylic polymers, acrylate polymers, carboxyvinyl polymers, copolymers of maleic anhydride and styrene, copolymers of maleic anhydride and ethylene, copolymers of maleic anhydride propylene or copolymers of maleic anhydride isobutylene), crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, diesters of polyglucan, polyacrylamides, polyacrylic acid, polyamides, polyethylene glycols, polyethylene oxides, poly(hydroxyalkyl methacrylate), polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, polystyrenes, polyvinylpyrrolidone, anionic and cationic hydrogels, and combinations thereof.

Non-limiting examples of suitable hydrophobic polymers include cellulose acetate butyrate, cellulose acetate ethylcarbamate, cellulose acetate heptanoate, cellulose acetate methylcarbamate, cellulose acetate octanoate, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate succinate, cellulose acetate trimaletate, cellulose acetaldehyde dimethyl acetate, cellulose butyrate, cellulose dimethylaminoacetate, cellulose disuccinate, cellulose dipalmitate, cellulose dicaprylate, cellulose propionate, cellulose propionate succinate, cellulose trioctanoate, cellulose tripropionate, cellulose trimellitate, cellulose tripalmitate, cellulose trivalerate, cellulose valerate palmitate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, ethylhydroxy ethylcellulose, hydroxy propyl methylcellulose phthalate, methyl cellulose, methyl ethyl cellulose, propyl cellulose, sodium carboxymethyl starch, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, methacrylic acid copolymers, methacrylic acid ester copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylate), poly(methacrylate), poly(methyl methacrylate), poly(ethylacrylate), poly(ethyl methacrylate), poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, ammonio methacrylate copolymers, lecithins, aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, hydrogenated vegetable oil, 12-hydroxystearyl alcohol, glyceryl

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monopalmitate, glyceryl dipalmitate, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, myristyl alcohol, stearic acid, stearyl alcohol, polyethyleneglycols, zein, shellac, bee's wax, carnauba wax, glyceryl behenate, Japan wax, paraffin, spermaceti, synthetic waxes, and combinations thereof.

(b) Methods of Producing Solid Dosage Forms

The solid dosage pharmaceutical compositions may be produced using any suitable method known in the art. The particular production method selected may depend on the desired type of solid dosage form and the desired release profile.

(i) Production of Tablet Compositions

The pharmaceutical compositions in the form of a tablet may be produced using any suitable method known in the art including but not limited to direct compression, wet granulation, dry granulation, and combinations thereof. In one embodiment, the morphinan-protected granules may be combined with the one or more carriers and granulated into tablet granules using any of the known granulation devices described previously. In this same embodiment, the tablet granules formed from the combination of the morphinan-protected granules and the one or more carriers may be optionally blended with one or more additional carriers including but not limited to lubricants, and the resulting tablet blend may be compressed into a tablet form. In another embodiment, one or more carriers incorporated into the tablet granules may include a release-controlling polymer to impart a modified release profile to the resulting tablet.

In yet another embodiment, a bilayer tablet may be formed by producing a first tablet blend and a second tablet blend using a tablet granulation and blending process similar to those previously described. In this embodiment, the first tablet blend may include a disintegrant in order to impart a rapid release profile to the resulting tablet produced using the first tablet blend. The second tablet blend of this embodiment may include a release-controlling polymer to impart a modified release profile to the resulting tablet produced using the second tablet blend. The first tablet blend and the second tablet blend may be loaded into a tableting device including but not limited to a bilayer tablet press, and pressed into a bilayer tablet in which the first layer may have a rapid release profile and the second layer may have a modified release profile.

In yet another embodiment, the morphinan-protected granules may be coated with a release-controlling polymer prior to incorporating the morphinan-protected granules into a solid tablet form in order to impart a modified release profile to the resulting tablet. In an additional embodiment, the solid tablet form may be coated with a release-controlling polymer to impart a modified release profile. Other combinations of the embodiments described above may be used to produce additional embodiments having a desired release profile or other desired performance characteristic including but not limited to masked taste, acceptable tongue-feel and mouth-feel, and enhanced stability.

(ii) Production of Capsule Compositions

The pharmaceutical compositions in the form of a capsule may be produced using any suitable method known in the art including but not limited to direct loading into two-piece telescoping hard capsules. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, and hard cellulose capsules. In one embodiment, the capsule form of the pharmaceutical compositions may be produced by loading the morphinan-protected granules in to the hard capsule and sealing the capsule. In other embodiments, the morphinan-protected granules may be coated with a release-controlling polymer to impart a modified release

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profile to the hard capsule composition. In yet other embodiments, a fraction of the morphinan-protected granules may be coated with a release-controlling polymer and combined with the remaining uncoated morphinan-protected granules prior to loading the granules into the hard capsule.

(VI) Exemplary Embodiments

Exemplary embodiments of a granule and a solid dose pharmaceutical composition are described below.

(a) Oxycodone-Protected Granule

An exemplary embodiment of a granule includes oxycodone, microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid. The overall composition of the exemplary oxycodone-protected granule embodiment is listed in Table 10 below. In this embodiment, the granules may be formed using the wet granulation method described in Example 5 below. In this embodiment, the oxycodone granules have a granule d₉₀ ranging from about 100 μm to about 400 μm, and contain less than about 2% water by weight.

(b) Bilayer Oxycodone/APAP Tablet

An exemplary embodiment of a solid dose pharmaceutical composition may be a bilayer tablet that includes the oxycodone-protected granules described above. The exemplary bilayer tablet may be formed using the method described in Example 2 below. The two layers of the bilayer tablet in this embodiment include an immediate release (IR) layer and a sustained release (SR) layer. The overall compositions of the IR layer and the sustained release layer of the exemplary bilayer tablet embodiment are listed in Table 1 below. The stability of the oxycodone in the exemplary bilayer tablet composition that incorporates oxycodone in a granular form is significantly better than a similar bilayer tablet composition that incorporates oxycodone in an unprotected powder form, as described in Example 2 below.

TABLE 1

Composition of Exemplary Oxycodone Bilayer Tablet Composition		
Compound	Dry Wt. (% total)	
	IR Layer	SR Layer
Protected oxycodone granules	2.99%	2.62%
APAP	77.73%	22.73%
MCC	4.82%	26.81%
Hydroxypropyl cellulose	7.71%	1.34%
Cross carmellose sodium	6.00%	
Silicon dioxide	0.50%	0.5%
Magnesium stearate	0.25%	1.0%
Polyethylene oxide polymer		45.0%

(c) Hydrocodone-Protected Granule

An exemplary embodiment of a granule includes hydrocodone, microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid. The overall composition of the exemplary hydrocodone-protected granule embodiment is listed in Table 13 below. In this embodiment, the granules may be formed using the wet granulation method described in Example 6 below. In this embodiment, the hydrocodone granules have a granule d₉₀ ranging from about 100 μm to about 400 μm after milling, and contain less than about 5% water by weight.

(d) Bilayer Hydrocodone/APAP Tablet

An exemplary embodiment of a solid dose pharmaceutical composition may be a bilayer tablet that includes the hydrocodone-protected granules described above. The exemplary

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bilayer tablet may be formed using the method described in Example 2 below. The two layers of the bilayer tablet in this embodiment include an immediate release (IR) layer and a sustained release (SR) layer. The overall compositions of the IR layer and the sustained release layer of the exemplary bilayer tablet embodiment are listed in Table 2 below. The stability of the hydrocodone in the exemplary bilayer tablet composition that incorporates hydrocodone in a granular form is significantly better than a similar bilayer tablet composition that incorporates hydrocodone in an unprotected powder form.

TABLE 2

Composition of Exemplary Hydrocodone Bilayer Tablet Composition		
Compound	Dry Wt. (% total)	
	IR Layer	SR Layer
Protected hydrocodone granules	2.99%	2.62%
APAP	77.73%	22.73%
MCC	4.82%	26.81%
Hydroxypropyl cellulose	7.71%	1.34%
Cross carmellose sodium	6.00%	
Silicon dioxide	0.50%	0.5%
Magnesium stearate	0.25%	1.0%
Polyethylene oxide polymer		45.0%

EXAMPLES

The following examples demonstrate various aspects of the invention.

Example 1

Incorporation of Protected Oxycodone Granules into Bilayer Tablet Composition

To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan granules into a solid dosage form, the following experiment was conducted.

Powdered oxycodone HCl, microcrystalline cellulose (MCC), and citric acid powder (an antioxidant) were mixed together and charged into a high-shear granulator. An aqueous solution containing pregelatinized starch (PGS) and Na₂EDTA (an antioxidant) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 2% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 μ m. The composition of the protected oxycodone granules is summarized in Table 3:

TABLE 3

Composition of Protected Oxycodone Granules	
Compound	Dry Weight (% tot. wt.)
Oxycodone HCl	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

The oxycodone-protected granules were divided into two groups to be incorporated into batches of immediate release (IR) granules and into batches of sustained release (SR) gran-

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ules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed protected oxycodone granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 4:

TABLE 4

Composition of IR and SR Granules		
Compound	Dry Wt. (% total wt.)	
	IR Layer	SR Layer
Protected oxycodone granules	16.1%	14.2%
APAP	67.8%	81.2%
MCC	5.0%	
Hydroxypropyl cellulose	8.1%	4.5%
Cross carmellose sodium	3.0%	

The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 5:

TABLE 5

Composition of IR and SR Blends		
Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	99.25%	
SR granules		52.30%
Silicon dioxide	0.50%	0.50%
Magnesium stearate	0.25%	0.10%
MCC		1.20%
Polyethylene oxide polymer		45.00%

The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 29% of the IR blend and about 71% the SR blend by weight.

The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Example 2

Oxidative Stability Assessment of Bilayer Tablet Composition

To assess the effect of incorporating a morphinan in the form of protected granules into a solid dosage therapeutic composition on the oxidative stability of the composition, the following experiment was conducted.

Unprotected bilayer tablets were formed using a process similar to that described in Example 1, except that powdered oxycodone HCl, rather than protected oxycodone granules, were incorporated into the IR and SR granules formed using

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the fluid bed granulation device. Protected bilayer tablets formed using protected oxycodone granules as described in Example 1 were also obtained. The unprotected bilayer tablets were similar in composition to the protected bilayer tablets, except that the unprotected bilayer tablets lacked anti-oxidant excipients and oxycodone-protected granules, although the overall oxycodone contents of the two formulations of bilayer tablet were comparable.

A batch of protected bilayer tablets and a batch of unprotected tablets were placed into an environmental chamber and exposed to accelerated stability conditions. In particular, all bilayer tablets were kept in the environmental chamber at a temperature of 55° C. and a relative humidity of 80% for a period of six days. For the remainder of the first month and for the duration of a second month, the bilayer tablets were exposed to a temperature of 40° C. and a relative humidity of 75%.

After six days, one month, and two months in the environmental chamber, samples of the protected and unprotected formulations were removed from the chamber and submitted to mass spectrographic analysis to determine the presence of three oxidative degradants of oxycodone: dihydroxy oxycodone, oxycodone n-oxide, and 10-hydroxy oxycodone. The results of these analyses are summarized in Table 6 below:

TABLE 6

Oxidative Stability of Unprotected vs. Protected Formulations of Bilayer Tablets								
Amount of Degradant Formed (% weight of oxycodone)								
Degradation Conditions			Di-hydroxy oxycodone		10-hydroxy oxycodone		Oxycodone n-oxide	
Time (days)	Temp. (° C.)	Relative Humidity (%)	Not Protected	Protected	Not Protected	Protected	Not Protected	Protected
6	55	80	0.20	0.00	0.04	0.00	0.12	0.03
30	40	75	0.05	0.01	0.01	0.00	0.12	0.01
60	40	75	0.11	0.02	0.03	0.00	0.21	0.03

The protected formulation of the bilayer tablets that incorporated the oxycodone-protected granules had significantly lower levels of all degradants after exposure to all environmental conditions. No 10-hydroxy oxycodone was measured at any environmental condition for the protected formulation of the bilayer tablet.

The results of this experiment demonstrated that the formation of oxidative degradants of oxycodone was significantly inhibited by the incorporation of the oxycodone in the form of protected granules. In particular, the bilayer tablets formed using the protected oxycodone granules were significantly more stable than similar bilayer tablets formed using unprotected oxycodone powder.

Example 3

Effect of Granule Composition on Oxidative Stability

To assess the effect of various granule compositions on the oxidative stability of the morphinan encapsulated in the granules, the following experiment was conducted.

Granules containing oxycodone and various combinations of excipients were formed using methods similar to those described in Example 1. The specific compositions of the granules are summarized in Table 7:

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TABLE 7

Composition of IR and SR Granules					
Compound	Granule Composition (% w/w)				
	1	2	3	5	6
Oxycodone	30	30	30	30	30
MCC	65	64.95	62.2	64.95	62.2
HPC	5	4.6	4.6		
BHA		0.05		0.05	
EDTA		0.4	0.4	0.4	0.4
Ascorbic Acid			2.8		2.8
PGS				4.6	4.6

For granule compositions 1, 2, and 3 the HPC and EDTA were dissolved in a granulation solution and applied to a dry mixture of the remaining ingredients. For granule compositions 5 and 6, the PGS and EDTA were dissolved in a granulations solution and applied to a dry mixture of the remaining ingredients.

The resulting granules were stored at accelerated stability conditions for a period of 4 weeks at 40° C. and 75% relative humidity. Samples of the granules were taken just before storage and after one, two, and four weeks of storage at

accelerated stability conditions and subjected to mass spectrographic analysis as described in Example 2 to determine the presence of oxidative degradants of oxycodone. The results of the analyses of the samples taken after four weeks of storage are summarized in Table 8 below:

TABLE 8

Oxidative Stability of Granule Formulations		
Composition	Impurity After 4 Weeks at Accelerated Degradation Conditions (% wt of oxycodone)	
	6-a-Oxycodol	Noroxycodone
1	0.11	0.01
2	0.11	0.02
3	0.33	0.13
5	0.11	0.00
6	0.29	0.14

The impurities for granule compositions 1, 2, and 5 were all of comparable low amounts, indicating that the granulation of the oxycodone resulted in a protective effect from oxidative degradation. This protective effect was achieved even in granule composition 1, which did not include any antioxidant excipients. However, granule compositions 3 and 6, which contained ascorbic acid, resulted in much higher levels of

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oxidative impurities after 4 weeks of storage at accelerated stability conditions, indicating that the ascorbic acid may produce oxidative products that result in the long-term degradation of the oxycodone.

The results of this experiment demonstrated the protective effect of granulation against the oxidative degradation of oxycodone, so long as ascorbic acid was not included in the granule composition.

Example 4

Effect of Granulation Composition on Oxidative
Stability of Solid Dose Oxycodone/APAP
Formulations

To assess the effect of encapsulation on the oxidative stability of the morphinan in various solid dose formulations, the following experiment was conducted.

Solid dose tablets were formed using the methods described in Example 2. The solid dose tablets contained the oxycodone either in the protected granular form described in Example 3, or as the same ingredients in a powdered form rather than as granules. In both cases, the oxycodone and excipients were combined with APAP and polyethylene oxide (PEO) polymer. Each tablet contained 10% of the oxycodone granule compositions described in Example 3, in either granulated or powdered form, 46.8% APAP, and 43.2% PEO polymer on a weight basis.

The protected and unprotected tablet formulations were stored at accelerated stability conditions for a period of 4 weeks at 40° C. and 75% relative humidity. Samples of the tablets were taken just before storage and after one, two, and four weeks of storage at accelerated stability conditions and subjected to mass spectrographic analysis as described in Example 2 to determine the presence of oxidative degradants of oxycodone. The results of these analysis of the samples taken after four weeks of storage are summarized in Table 9 below:

TABLE 9

Effect of Granulation on Oxidative Stability of Tablet Formulations				
Composition Combined	Impurity After 4 Weeks at Accelerated Degradation Conditions (% wt of oxycodone)			
	6-a-Oxycodol		Noroxycodone	
with APAP	Protected granules	Unprotected	Protected Granules	Unprotected
1	0.20	.74	0.03	.27
2	0.22	.51	0.05	.28
3	0.60	1.25*	0.11	.14*
5	0.17	.49	0.01	.18

*measured at two weeks after storage

All of the protected tablet formulations, in which the oxycodone was granulated using methods similar to those described in Example 1 formed significantly lower levels of impurities after storage for 4 weeks at accelerated stability conditions compared to tablets containing non-granulated oxycodone and the same excipients

The results of this experiment demonstrated that granulating the oxycodone and excipients prior to incorporating the granules in a tableting process resulted in tablets with superior stability compared to tablets formed using the same oxy-

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codone and excipients in a loose powder form, independent of the particular composition of excipients in the formulation.

Example 5

Incorporation of Protected Oxycodone Granules into
Bilayer Tablet Composition

To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan granules into a solid dosage form, the following experiment was conducted to prepare a 7.5 mg oxycodone/325 mg acetaminophen tablet.

Powdered oxycodone HCl, microcrystalline cellulose (MCC), pregelatinized starch (PGS), Na₂EDTA (an antioxidant), and citric acid powder (an antioxidant) were charged into a high-shear granulator and mixed together. An aqueous solution containing pregelatinized starch (PGS) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 5% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 µm after milling. The composition of the oxycodone-protected granules is summarized in Table 10:

TABLE 10

Composition of Protected Oxycodone Granules	
Compound	Dry Weight (% tot. wt.)
Oxycodone HCl	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

The oxycodone-protected granules were divided into two groups to be incorporated into batches of immediate release (IR) granules and into batches of sustained release (SR) granules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed oxycodone-protected granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 11:

TABLE 11

Composition of IR and SR Granules		
Compound	Dry Wt. (% total wt.)	
	IR Granules	SR Granules
Protected oxycodone granules	3.10%	9.79%
APAP	80.65%	84.81%
MCC	5.0%	
Hydroxypropyl cellulose	8.0%	5.0%
Cross carmellose sodium	3.0%	
Silicon Dioxide	0.25%	0.4%

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The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 12:

TABLE 12

Composition of IR and SR Blends		
Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	96.38%	
SR granules		26.80%
Croscarmellose Sodium	3.11%	
Silicon dioxide	0.26%	0.39%
Magnesium stearate	0.25%	1.0%
MCC		26.81%
Polyethylene oxide polymer		45.00%

The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 23% of the IR blend and about 77% the SR blend by weight.

The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Example 6

Incorporation of Protected Hydrocodone Granules into Bilayer Tablet Composition

To demonstrate the feasibility of forming protected morphinan granules and incorporating the protected morphinan granules into a solid dosage form, the following experiment was conducted to prepare a 7.5 mg hydrocodone/325 mg acetaminophen tablet.

Powdered hydrocodone bitartrate, microcrystalline cellulose (MCC), pregelatinized starch (PGS) and citric acid powder (an antioxidant) were mixed together and charged into a high-shear granulator. An aqueous solution containing pregelatinized starch (PGS) and Na₂EDTA (an antioxidant) was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 5% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 µm after milling. The composition of the protected hydrocodone granules is summarized in Table 13:

TABLE 13

Composition of Protected Hydrocodone Granules	
Compound	Dry Weight (% tot. wt.)
Hydrocodone bitartrate	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

The hydrocodone-protected granules were divided into two groups to be incorporated into batches of immediate release (IR) granules and into batches of sustained release

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(SR) granules used to form the IR and SR Layers of a bilayer tablet, respectively. Both the IR granules and the SR granules were formed using separate fluid bed granulation processes. In each process, the previously-formed protected hydrocodone granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and SR granules in a second batch. The composition of the resulting IR and SR granules are summarized in Table 14:

TABLE 14

Composition of IR and SR Granules		
Compound	Dry Wt. (% total wt.)	
	IR Granules	SR Granules
Protected hydrocodone granules	3.10%	9.79%
APAP	80.65%	84.81%
MCC	5.0%	
Hydroxypropyl cellulose	8.0%	5.0%
Cross carmellose sodium	3.0%	
Silicon Dioxide	0.25%	0.4%

The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the SR particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the SR blend are summarized in Table 15:

TABLE 15

Composition of IR and SR Blends		
Compound	Dry Wt. (% total wt.)	
	IR Blend	SR Blend
IR granules	96.38%	
SR granules		26.80%
Croscarmellose Sodium	3.11%	
Silicon dioxide	0.26%	0.39%
Magnesium stearate	0.25%	1.0%
MCC		26.81%
Polyethylene oxide polymer		45.00%

The IR blend and the SR blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 23% of the IR blend and about 77% the SR blend by weight.

The results of this experiment demonstrated that protected morphinan granules could be formed using a process of high shear wet granulation and incorporated into a solid oral therapeutic composition.

Having described the invention in detail, it will be apparent that modifications and variations are possible. Those of skill in the art should, in light of the present disclosure, appreciate that many changes could be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth is to be interpreted as illustrative and not in a limiting sense.

What is claimed is:

1. A solid dosage pharmaceutical composition comprising:
 - (a) a plurality of granules containing a pharmaceutically acceptable salt of oxycodone, wherein the granules are

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substantially resistant to oxidative degradation of the pharmaceutically acceptable salt of oxycodone; and
(b) an additional active ingredient,

wherein the granules comprise an interior region substantially comprising the pharmaceutically acceptable salt of oxycodone and an exterior region substantially comprising at least one excipient;

wherein the granule contains less than about 0.5% w/w of the total mass of the pharmaceutically acceptable salt of oxycodone of each of any one or more of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone N-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

2. A solid dosage pharmaceutical composition of claim 1, wherein the additional active ingredient is acetaminophen.

3. A solid dosage pharmaceutical composition of claim 1, wherein the at least one excipient is chosen from the group consisting of a binder, a filler, an antioxidant, a chelating agent, and combinations thereof.

4. A solid dosage pharmaceutical composition of claim 1, further comprising at least one additional excipient selected from the group consisting of pH adjusting agents, antimicrobial agents, and combinations thereof.

5. A solid dosage pharmaceutical composition of claim 1, wherein the composition further comprises microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid.

6. A solid dosage pharmaceutical composition of claim 1, wherein the composition further comprises a hydrophilic polymer.

7. A solid dosage pharmaceutical composition of claim 6, wherein the hydrophilic polymer is selected from the group consisting of cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose ethers, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, nitrocellulose, crosslinked starch, agar, casein, chitin, collagen, gelatin, maltose, mannitol, maltodextrin, pectin, pullulan, sorbitol, xylitol, polysaccharides, ammonia alginate, sodium alginate, calcium alginate, potassium alginate, propylene glycol alginate, alginate sodium carmellose, calcium carmellose, carrageenan, fucoidan, furcellaran, arabicgum, carrageensgum, ghaftigum, guar gum, karayagum, locust beangum, okragum, tragacanthgum, scleroglucangum, xanthangum, hypnea, laminaran, acrylic polymers, acrylate polymers, carboxyvinyl polymers, copolymers of maleic anhydride and styrene, copolymers of maleic anhydride and ethylene, copolymers of maleic anhydride propylene or copolymers of maleic anhydride isobutylene, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, diesters of polyglucan, polyacrylamides, polyacrylic acid, polyamides, polyethylene glycols, polyethylene oxides, poly(hydroxyalkyl methacrylate), polyvinyl acetate, polyvinyl alcohol, polyvinyl chloride, polystyrenes, polyvinylpyrrolidone, anionic and cationic hydrogels, and combinations thereof.

8. A solid dosage pharmaceutical composition of claim 1, wherein the composition further comprises a hydrophobic polymer.

9. A solid dosage pharmaceutical composition of claim 8, wherein the hydrophobic polymer is selected from the group consisting of cellulose acetate butyrate, cellulose acetate ethylcarbamate, cellulose acetate heptanoate, cellulose acetate methylcarbamate, cellulose acetate octanoate, cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate succinate, cellulose acetate trimaleate, cellulose acetaldehyde dimethyl acetate, cellulose butyrate, cellulose dimethylaminoacetate, cellulose disuccinate, cellulose dipalmitate, cellulose dicaprylate, cellulose propionate, cel-

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lulose propionate succinate, cellulose trioctanoate, cellulose tripropionate, cellulose trimellitate, cellulose tripalmitate, cellulose trivalerate, cellulose valerate palmitate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, ethylhydroxy ethylcellulose, hydroxy propyl methylcellulose phthalate, methyl cellulose, methyl ethyl cellulose, propyl cellulose, sodium carboxymethyl starch, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, methacrylic acid copolymers, methacrylic acid ester copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylate), poly(methacrylate), poly(methyl methacrylate), poly(ethylacrylate), poly(ethyl methacrylate), poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, ammonio methacrylate copolymers, lecithins, aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, hydrogenated vegetable oil, 12-hydroxystearyl alcohol, glyceryl monopalmitate, glyceryl dipalmitate, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, myristyl alcohol, stearic acid, stearyl alcohol, polyethylenglycols, zein, shellac, bee's wax, carnauba wax, glyceryl behenate, Japan wax, paraffin, spermaceti, synthetic waxes, and combinations thereof.

10. A solid dosage pharmaceutical composition of claim 1, wherein the composition is a bilayer tablet.

11. A solid dosage pharmaceutical composition comprising:

- (a) an immediate release layer; and
- (b) a sustained release layer,

wherein both the immediate release layer and the sustained release layer comprise a plurality of granules containing a pharmaceutically acceptable salt of oxycodone, wherein the granules containing the pharmaceutically acceptable salt of oxycodone comprise an interior region substantially comprising the pharmaceutically acceptable salt of oxycodone and an exterior region substantially comprising at least one excipient,

wherein the granule contains less than about 0.5% w/w of the total mass of the pharmaceutically acceptable salt of oxycodone of each of any one or more of a degradant selected from 10-hydroxy oxycodone, di-hydroxy oxycodone, and oxycodone n-oxide after being stored for 6 months at 40° C. and 75% relative humidity.

12. A solid dosage pharmaceutical composition of claim 11, wherein the at least one excipient is chosen from the group consisting of a binder, a filler, an antioxidant, a chelating agent, and combinations thereof.

13. A solid dosage pharmaceutical composition of claim 11, further comprising at least one additional excipient selected from the group consisting of pH adjusting agents, antimicrobial agents, and combinations thereof.

14. A solid dosage pharmaceutical composition of claim 11, wherein the at least one excipient is chosen from the group consisting of microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid.

15. A solid dosage pharmaceutical composition of claim 11, wherein the composition further comprises a hydrophilic polymer.

16. A solid dosage pharmaceutical composition of claim 15, wherein the hydrophilic polymer is polyethylene oxide.

17. A solid dosage pharmaceutical composition of claim 11, wherein the composition further comprises an additional active ingredient.

18. A solid dosage pharmaceutical composition of claim 17, wherein the additional active ingredient is acetaminophen.

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19. A solid dosage pharmaceutical composition comprising:

(a) a plurality of granules containing a pharmaceutically acceptable salt of hydrocodone, wherein the granules are substantially resistant to oxidative degradation of hydrocodone; and

(b) an additional active ingredient,

wherein the granules containing the pharmaceutically acceptable salt of hydrocodone comprise an interior region substantially comprising the pharmaceutically acceptable salt of hydrocodone and an exterior region substantially comprising at least one excipient;

wherein the granule contains less than about 0.5% w/w of the total mass of the pharmaceutically acceptable salt of hydrocodone of each of any one or more of a degradant selected from hydrocodone-N-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

20. A solid dosage pharmaceutical composition of claim 19, wherein the additional active ingredient is acetaminophen.

21. A solid dosage pharmaceutical composition of claim 19, wherein the at least one excipient is chosen from the group consisting of a binder, a filler, an antioxidant, a chelating agent, and combinations thereof.

22. A solid dosage pharmaceutical composition of claim 19, further comprising at least one additional excipient selected from the group consisting of pH adjusting agents, antimicrobial agents, and combinations thereof.

23. A solid dosage pharmaceutical composition of claim 19, wherein the composition further comprises microcrystalline cellulose, pregelatinized starch, Na₂EDTA, and citric acid.

24. A solid dosage pharmaceutical composition of claim 19, wherein the composition further comprises a hydrophilic polymer.

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25. A solid dosage pharmaceutical composition of claim 19, wherein the composition further comprises a hydrophobic polymer.

26. A solid dosage pharmaceutical composition of claim 19, wherein the composition is a bilayer tablet.

27. A solid dosage pharmaceutical composition comprising:

(a) an immediate release layer; and

(b) a sustained release layer,

wherein both the immediate release layer and the sustained release layer comprise a plurality of granules containing a pharmaceutically acceptable salt of hydrocodone,

wherein the granules containing the pharmaceutically acceptable salt of hydrocodone comprise an interior region substantially comprising the pharmaceutically acceptable salt of hydrocodone and an exterior region substantially comprising at least one excipient,

wherein the granule contains less than about 0.5% w/w of the total mass of the pharmaceutically acceptable salt of hydrocodone of each of any one or more of a degradant selected from hydrocodone-n-oxide and hydrocodone aldol dimer after being stored for 6 months at 40° C. and 75% relative humidity.

28. A solid dosage pharmaceutical composition of claim 27, wherein the at least one excipient is chosen from the group consisting of a binder, a filler, an antioxidant, a chelating agent, and combinations thereof.

29. A solid dosage pharmaceutical composition of claim 27, wherein the composition further comprises an additional active ingredient.

30. A solid dosage pharmaceutical composition of claim 29, wherein the additional active ingredient is acetaminophen.

* * * * *

EXHIBIT E

US008992975B2

(12) **United States Patent**
Devarakonda et al.

(10) **Patent No.:** **US 8,992,975 B2**
(45) **Date of Patent:** ***Mar. 31, 2015**

(54) **COMBINATION COMPOSITION
 COMPRISING OXYCODONE AND
 ACETAMINOPHEN FOR RAPID ONSET AND
 EXTENDED DURATION OF ANALGESIA**

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 (US)

(72) Inventors: **Krishna R. Devarakonda**, St. Louis,
 MO (US); **Michael J. Giuliani**, Creve
 Coeur, MO (US); **Vishal K. Gupta**,
 Hillsborough, NJ (US); **Ralph A.**
Heasley, Webster Groves, MO (US);
Susan Shelby, Town and Country, MO
 (US)

(73) Assignee: **Mallinckrodt LLC**, Hazelwood, MO
 (US)

(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 0 days.
 This patent is subject to a terminal dis-
 claimer.

(21) Appl. No.: **14/109,052**

(22) Filed: **Dec. 17, 2013**

(65) **Prior Publication Data**
 US 2014/0170217 A1 Jun. 19, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/473,563, filed on
 May 16, 2012, now Pat. No. 8,658,631.

(60) Provisional application No. 61/487,047, filed on May
 17, 2011, provisional application No. 61/537,527,
 filed on Sep. 21, 2011, provisional application No.
 61/606,850, filed on Mar. 5, 2012.

(51) **Int. Cl.**
A61K 31/485 (2006.01)
A61K 9/24 (2006.01)
A61K 31/167 (2006.01)
A61K 9/20 (2006.01)

(52) **U.S. Cl.**
 CPC **A61K 9/209** (2013.01); **A61K 31/167**
 (2013.01); **A61K 31/485** (2013.01); **A61K**
9/2013 (2013.01); **A61K 9/2054** (2013.01)
 USPC **424/468**

(58) **Field of Classification Search**
 None
 See application file for complete search history.

Primary Examiner — Jeffrey S Lundgren
Assistant Examiner — Zenab Olabowale
 (74) *Attorney, Agent, or Firm* — Mayer Brown LLP

(57) **ABSTRACT**

The present disclosure provides an extended release phar-
 maceutical composition comprising oxycodone and acetami-
 nophen that provides a rapid onset of analgesia, and reduced
 levels of acetaminophen near the end of the dosing interval.
 Also provided are methods for reducing the risk of acetami-
 nophen-induced hepatic damage in a subject being treated
 with an acetaminophen containing composition, as well as
 methods for treating pain in a subject in need thereof.

30 Claims, 49 Drawing Sheets
(29 of 49 Drawing Sheet(s) Filed in Color)

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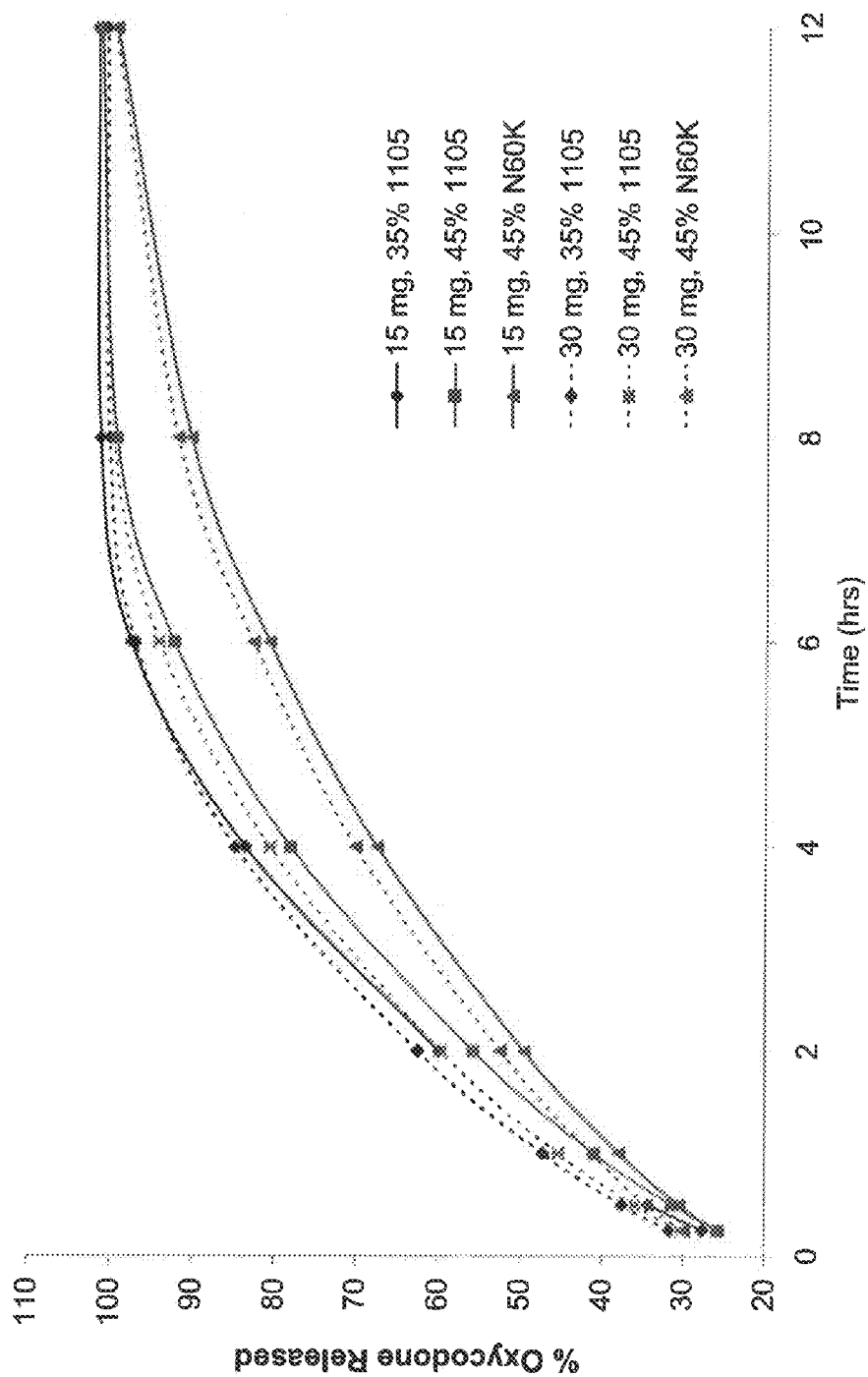


FIG. 1

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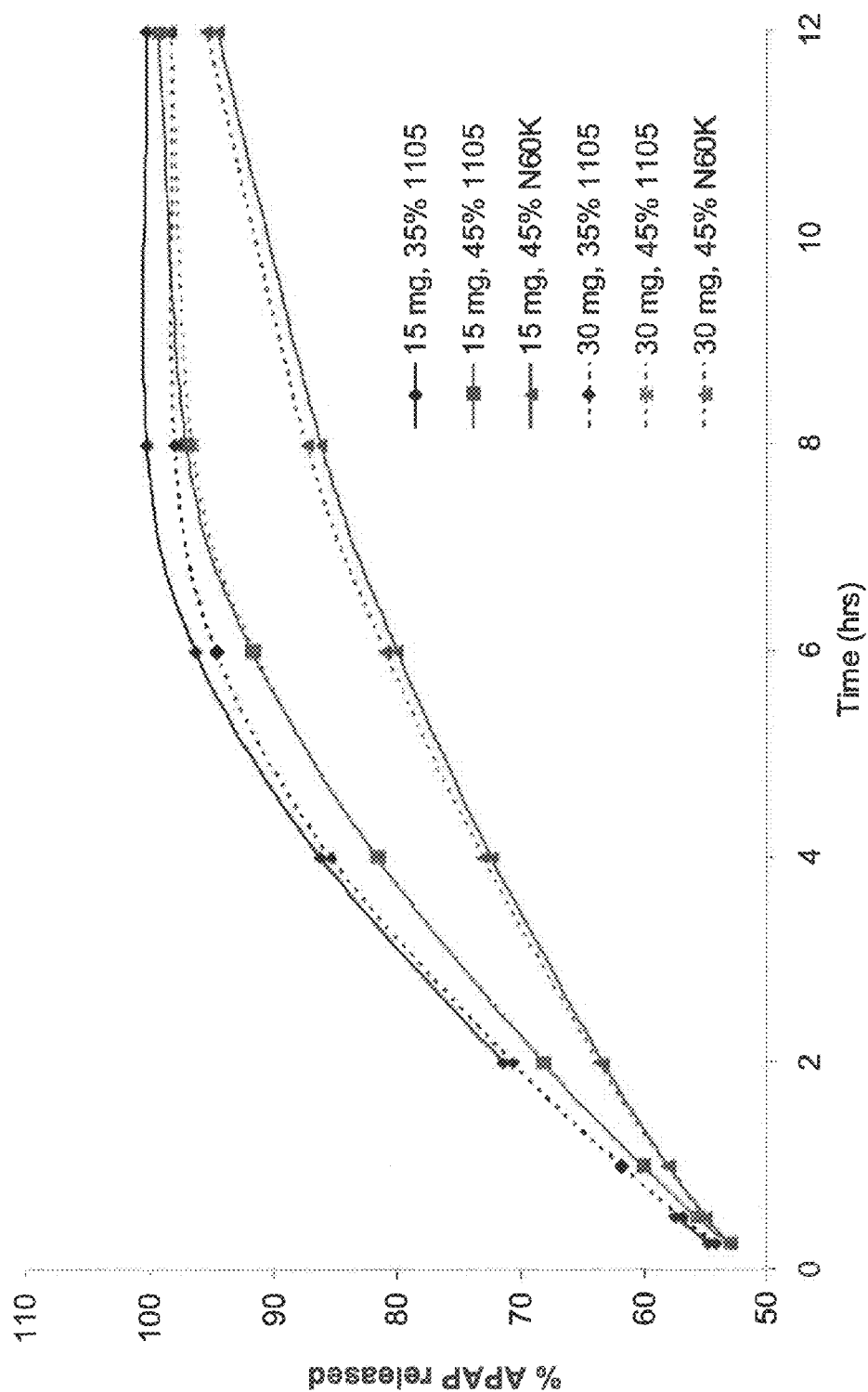


FIG. 2

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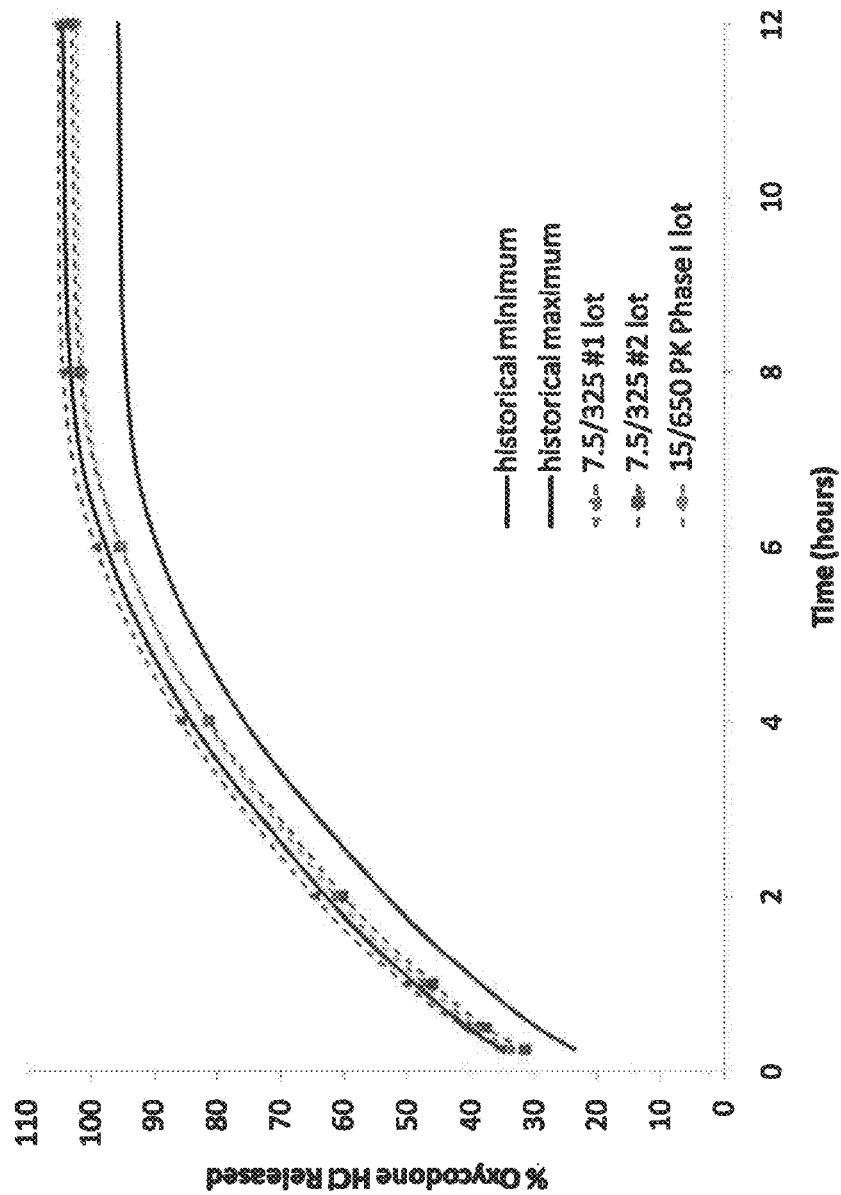


FIG. 3

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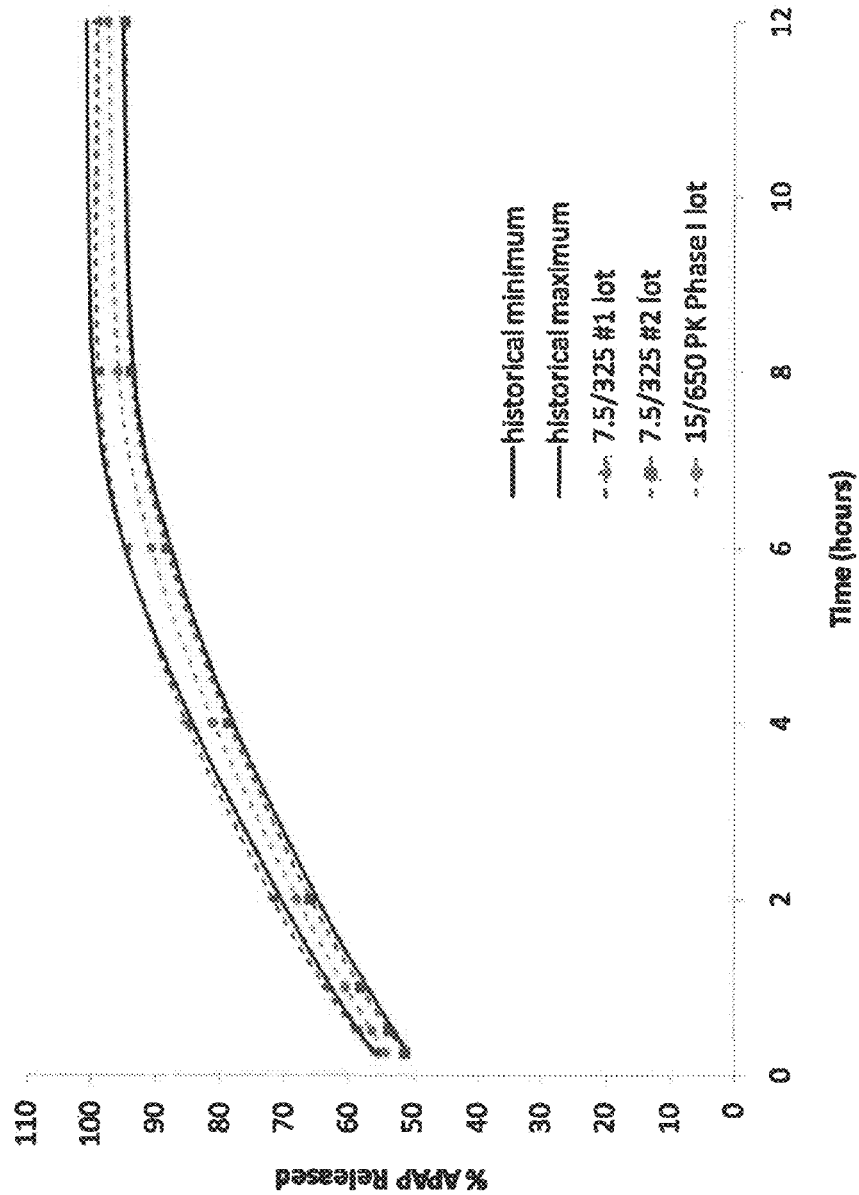


FIG. 4

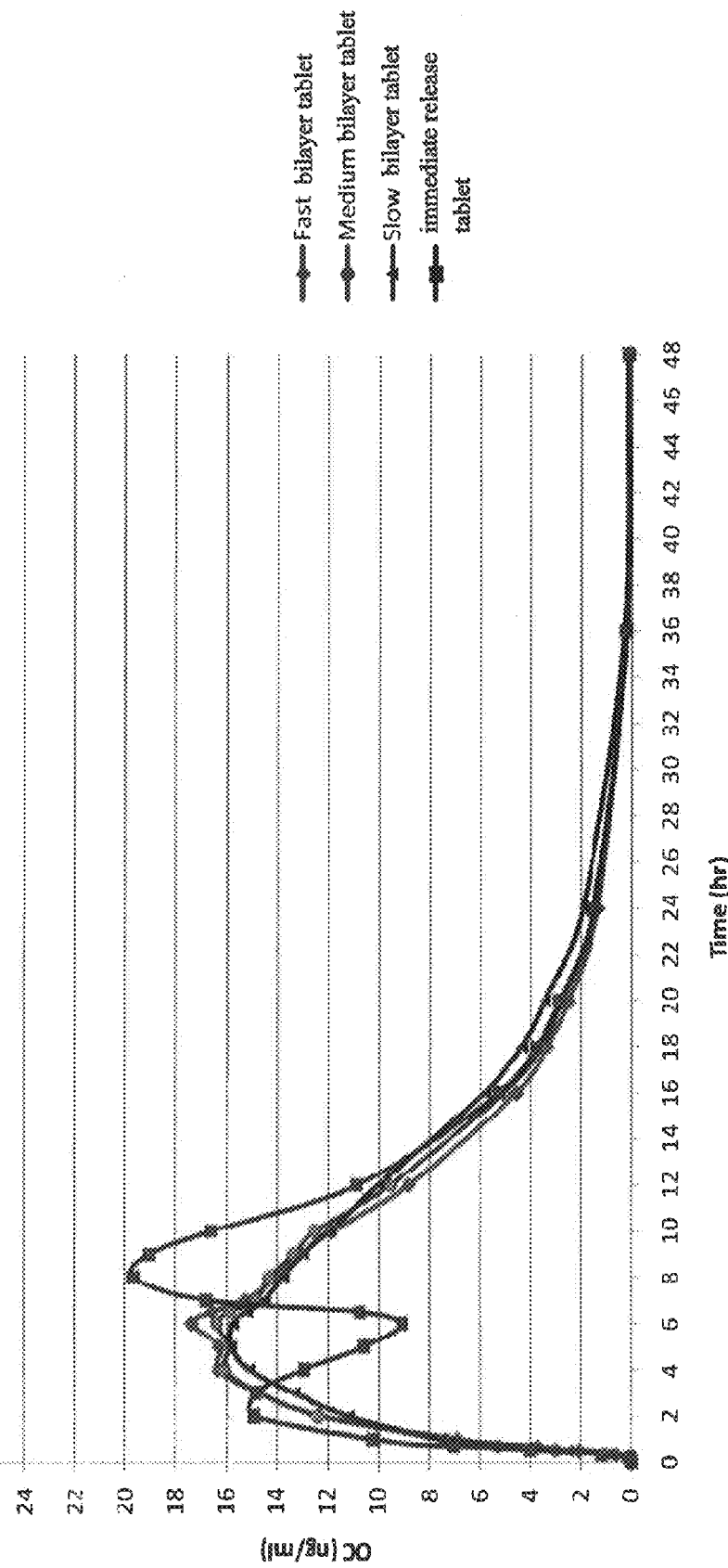


FIG. 5

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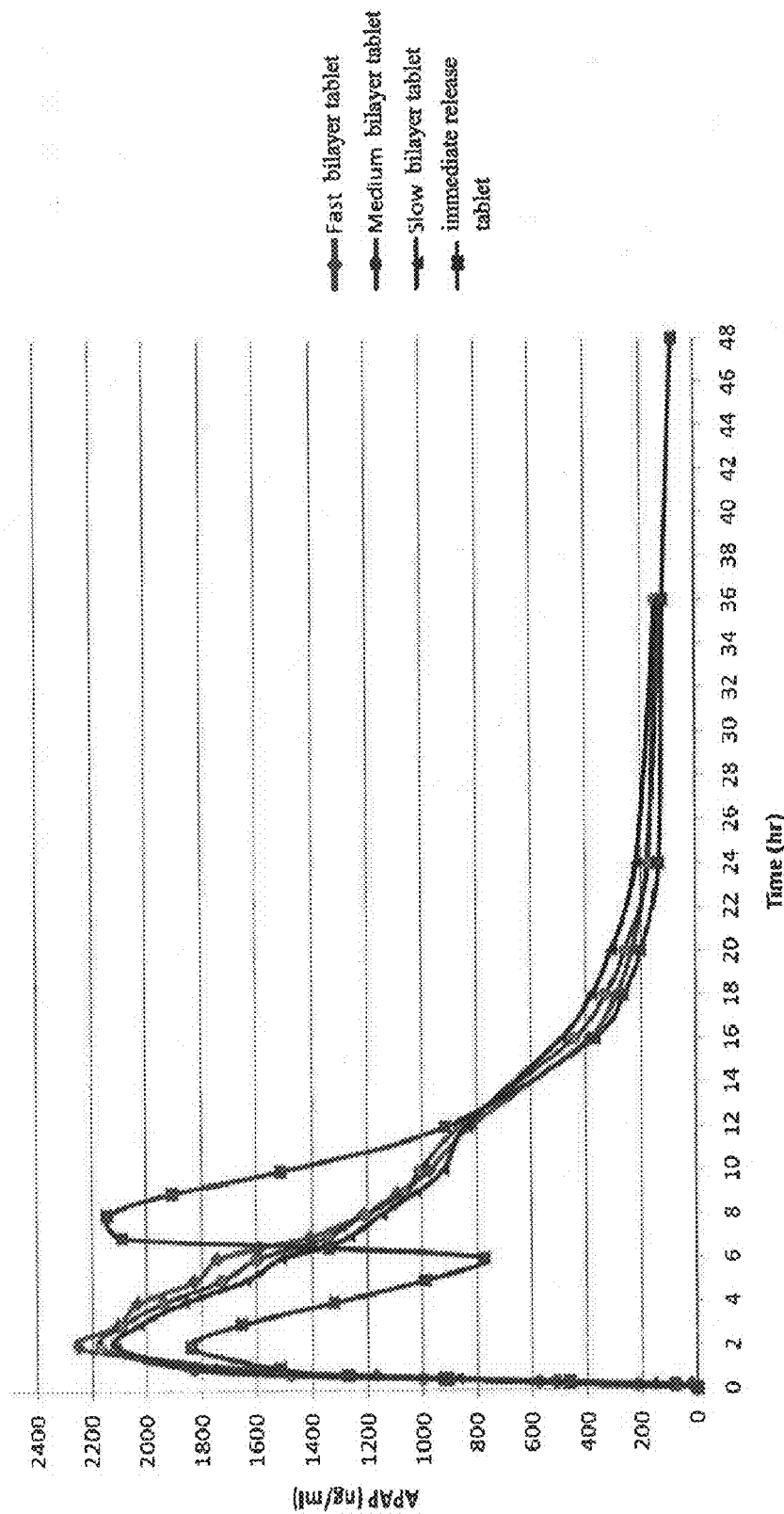


FIG. 6

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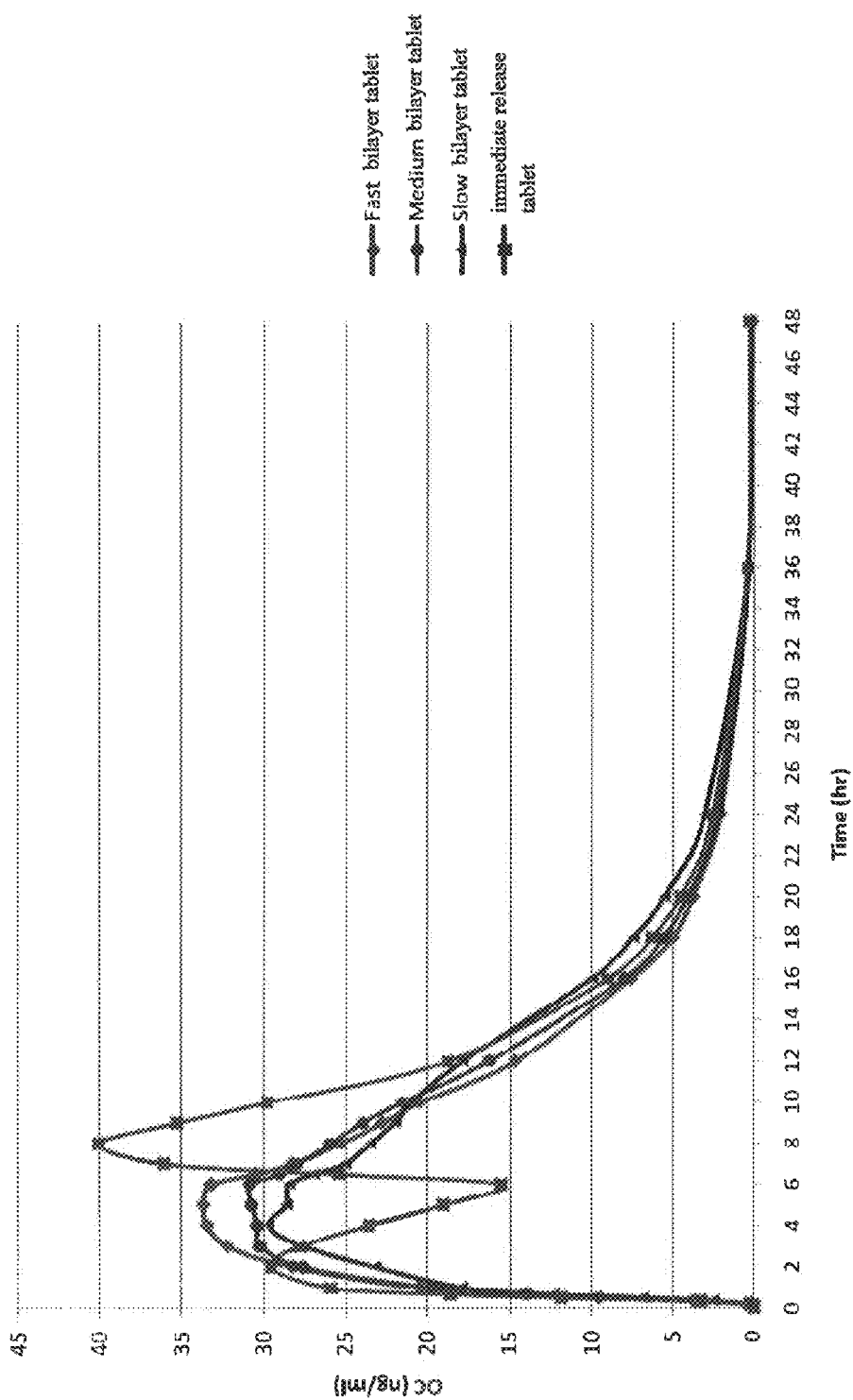


FIG. 7

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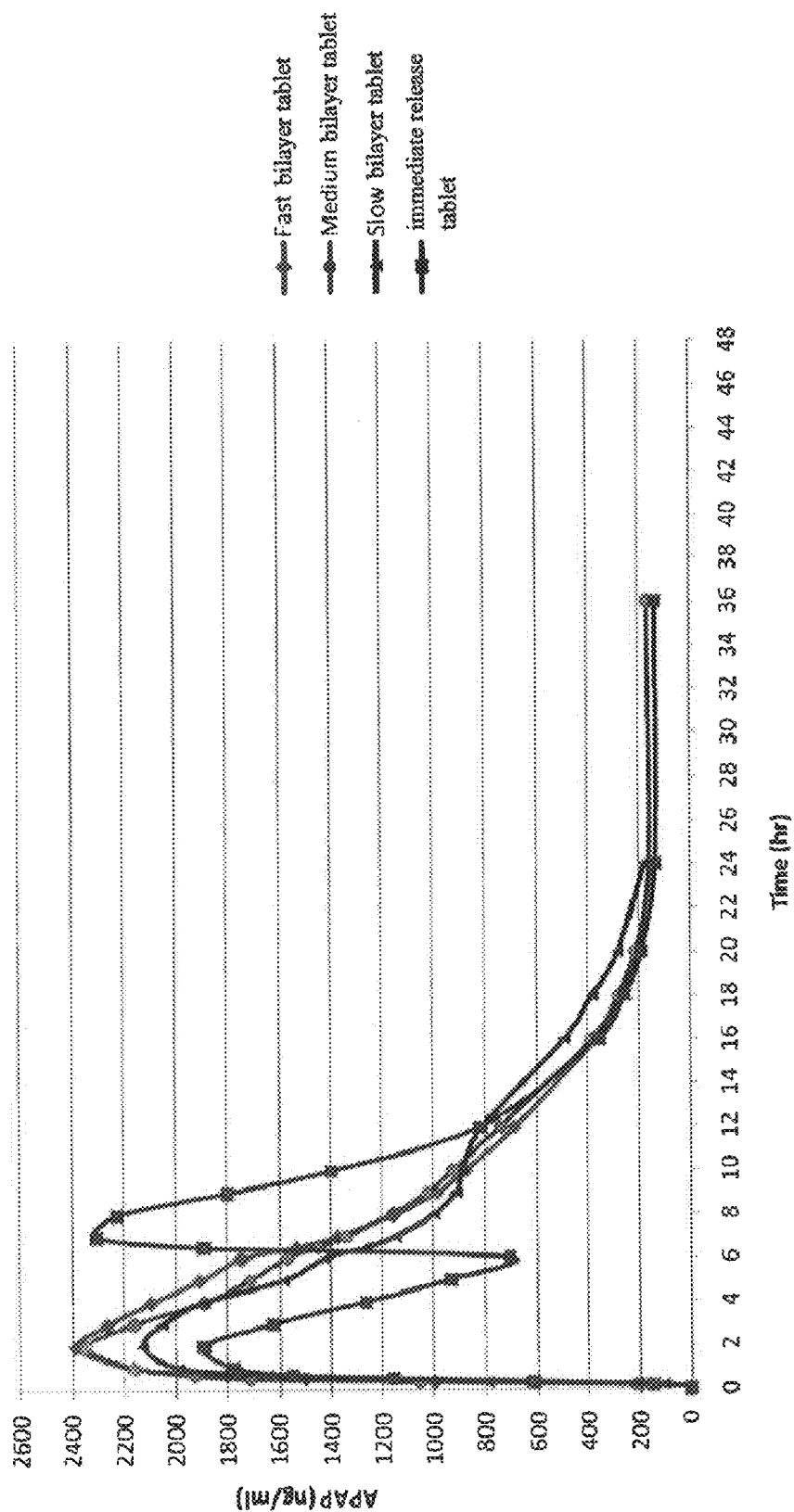


FIG. 8

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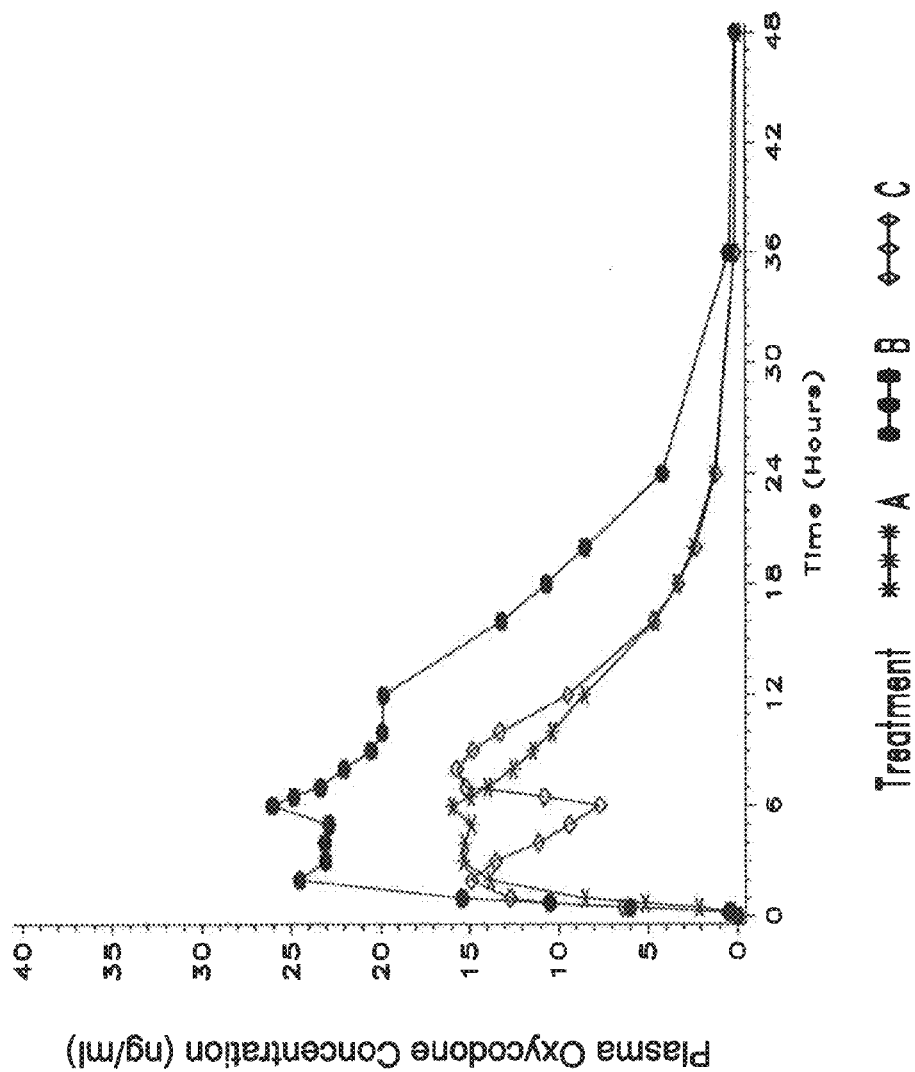


FIG. 9

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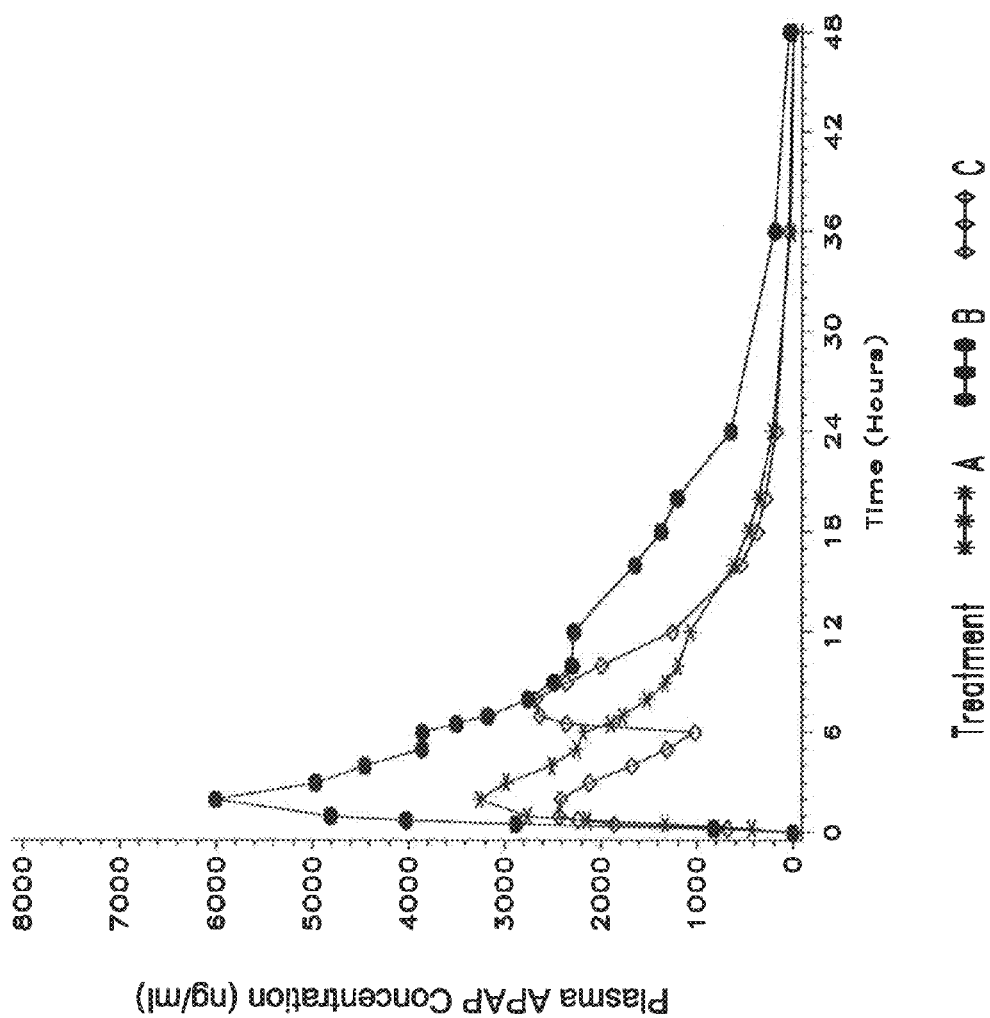


FIG. 10

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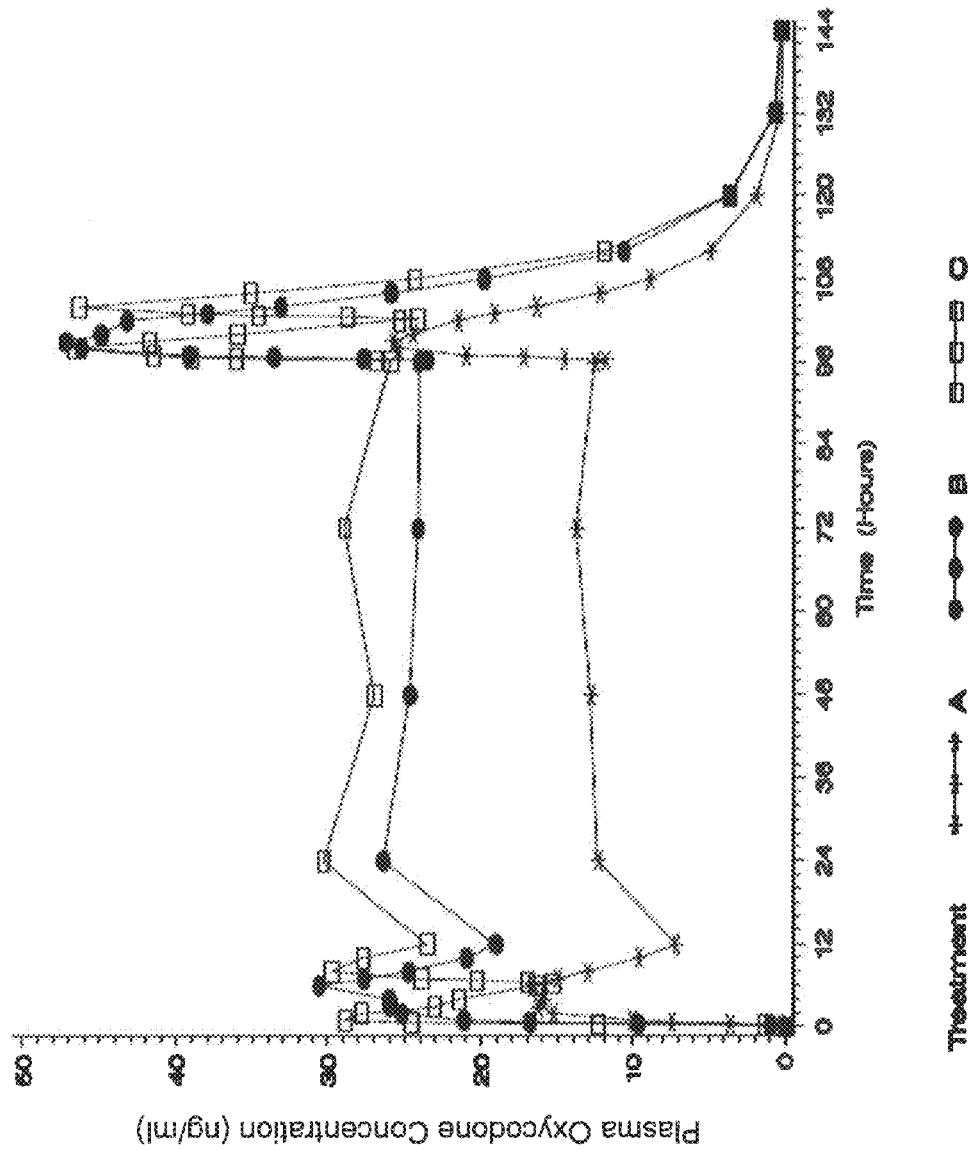


FIG. 11

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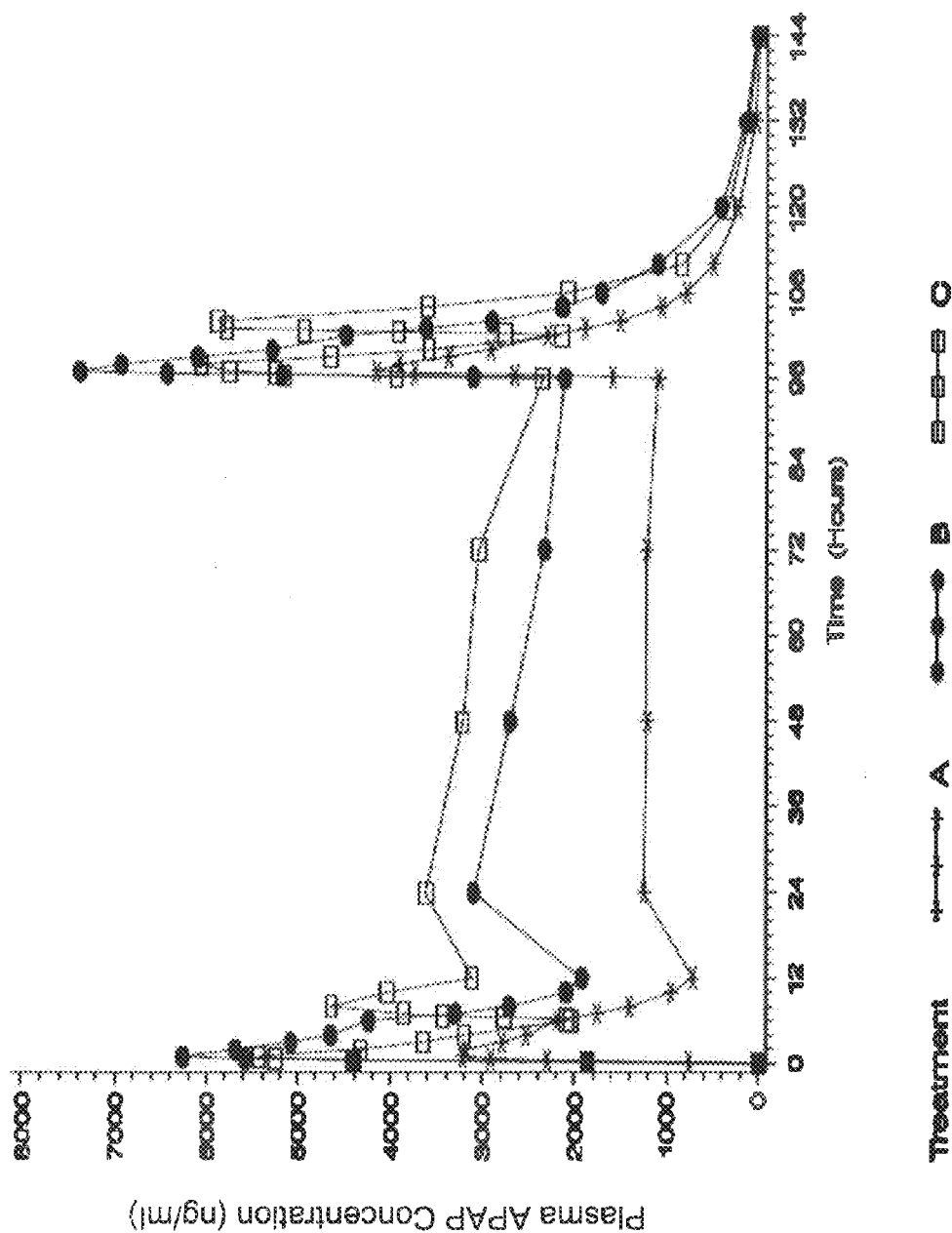


FIG. 12

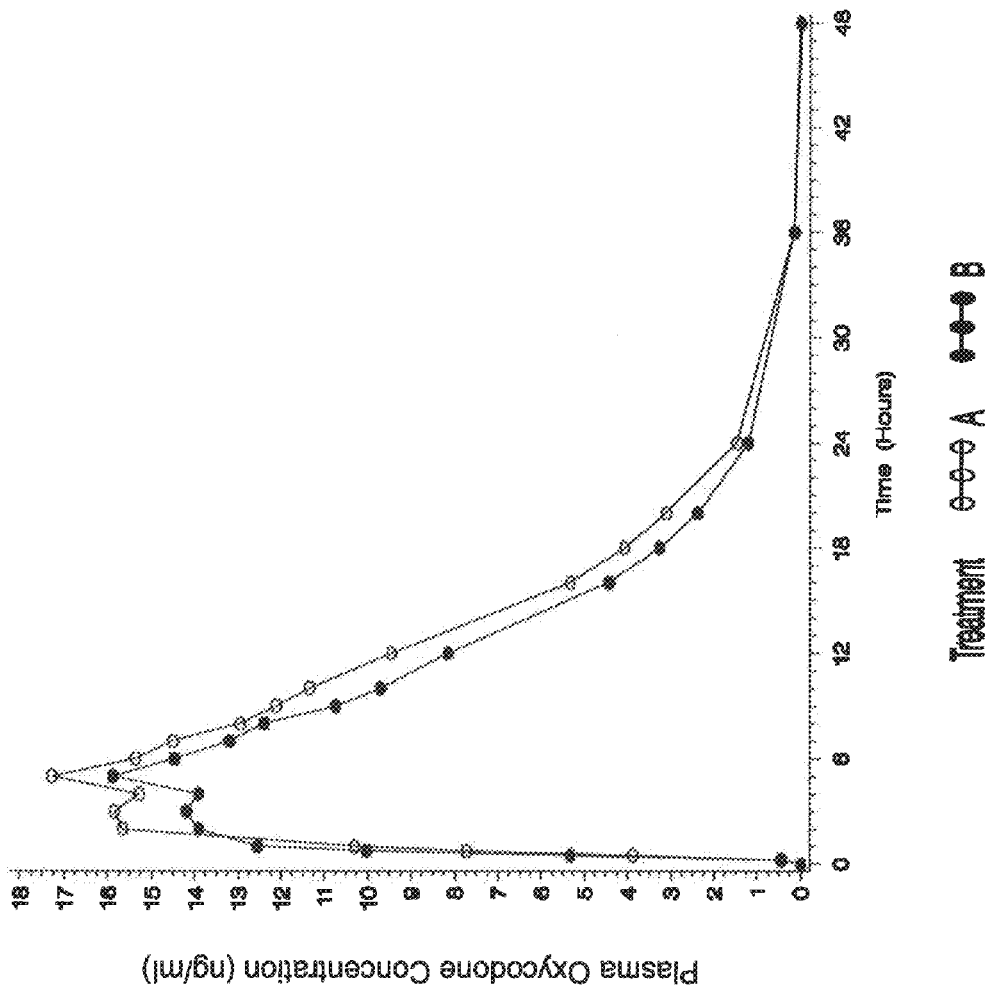


FIG. 13

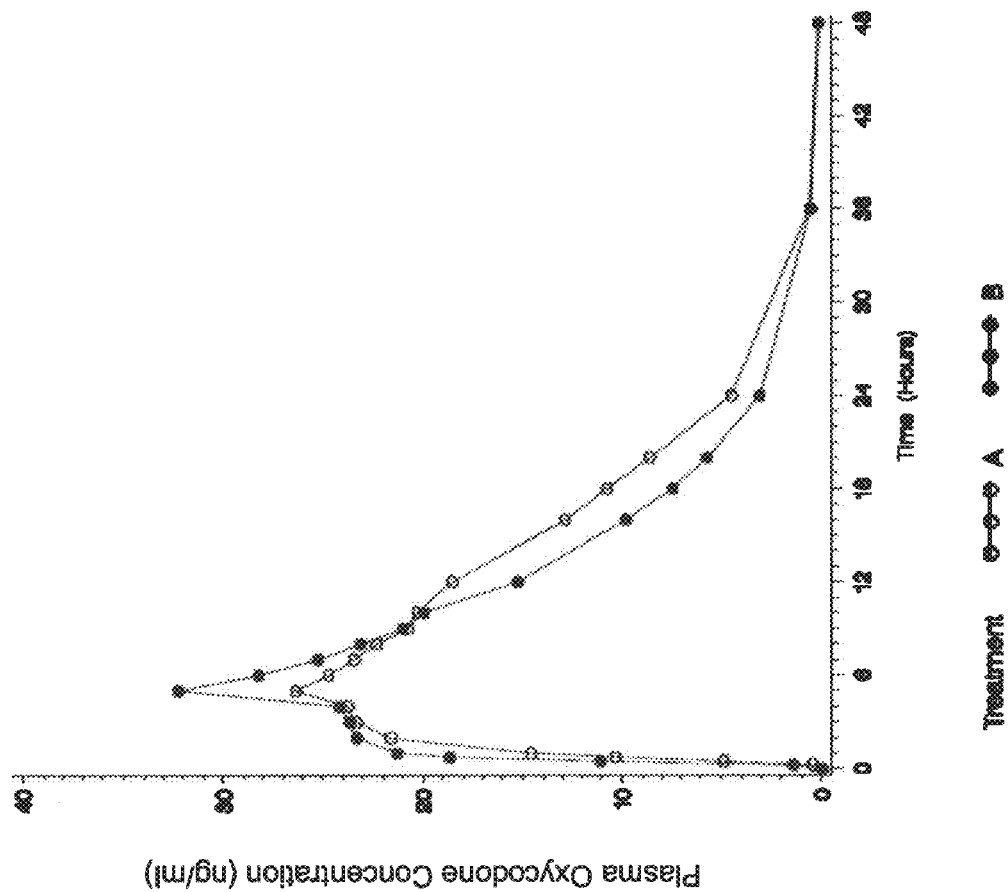


FIG. 14

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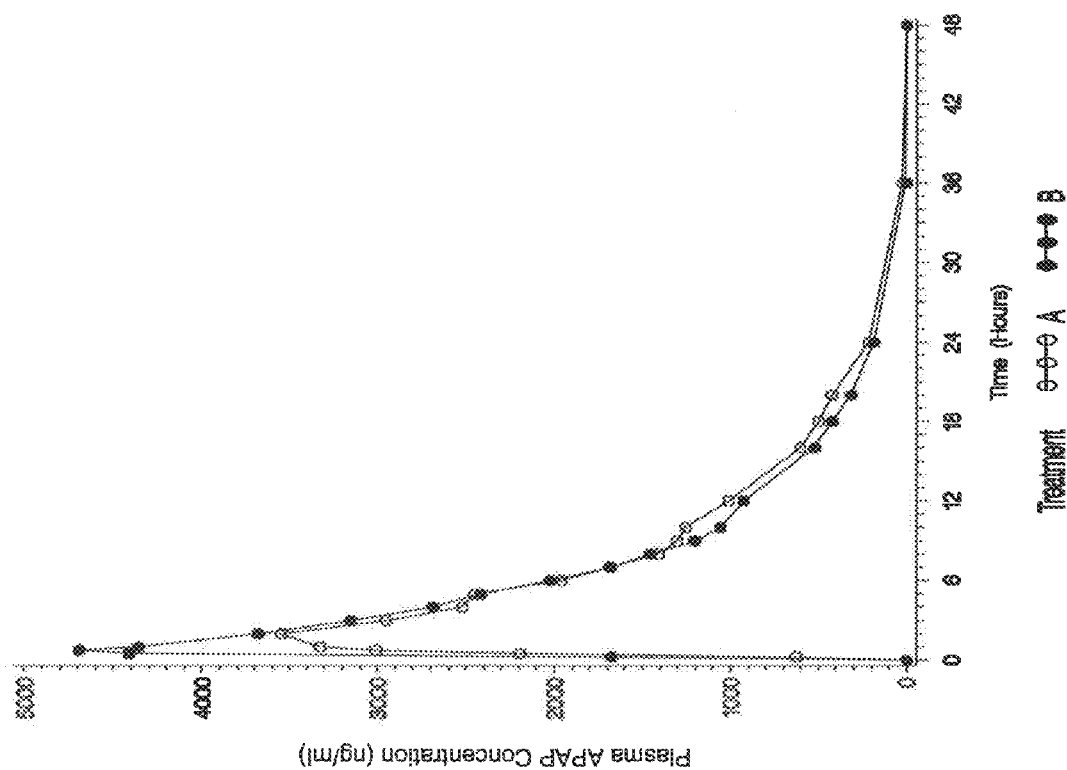


FIG. 15

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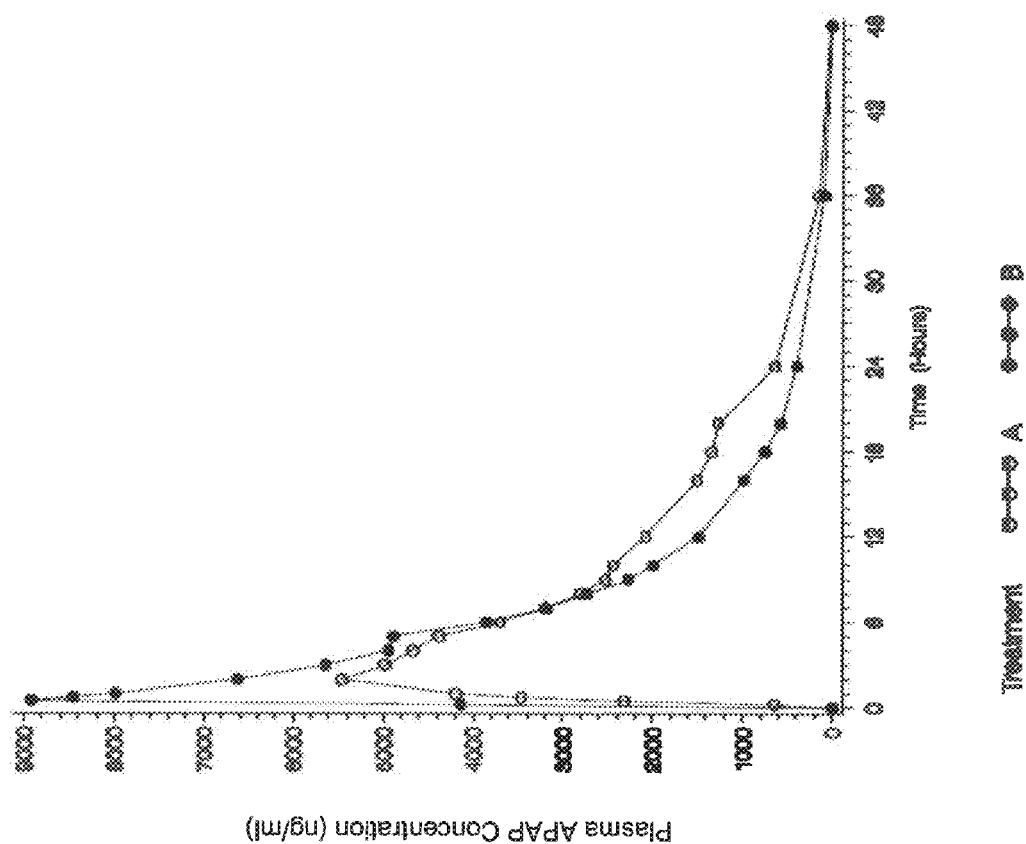


FIG. 16

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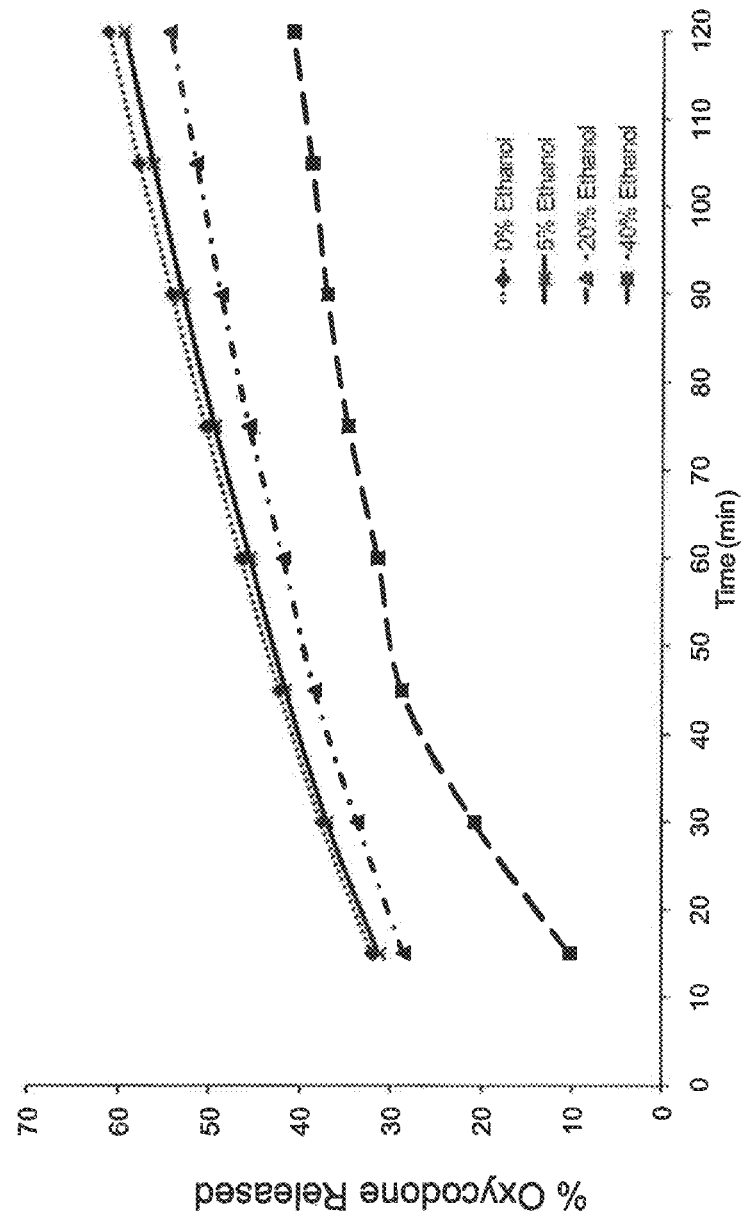


FIG. 17

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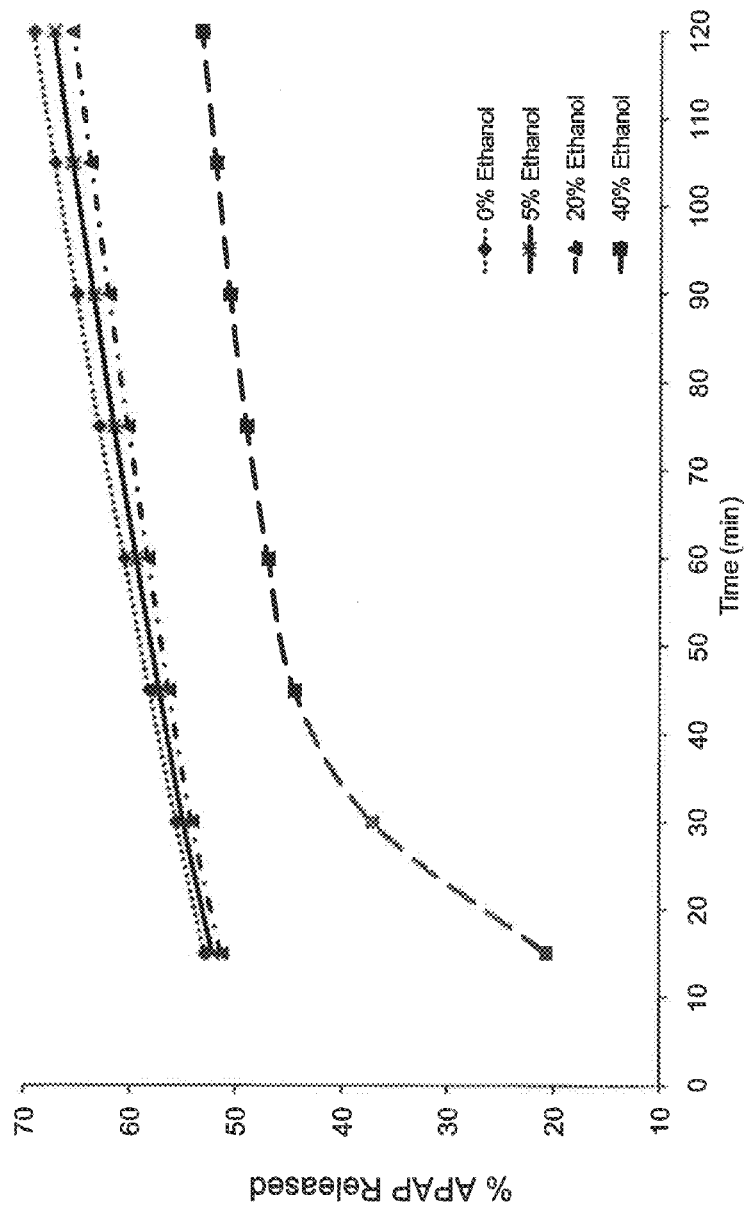


FIG. 18

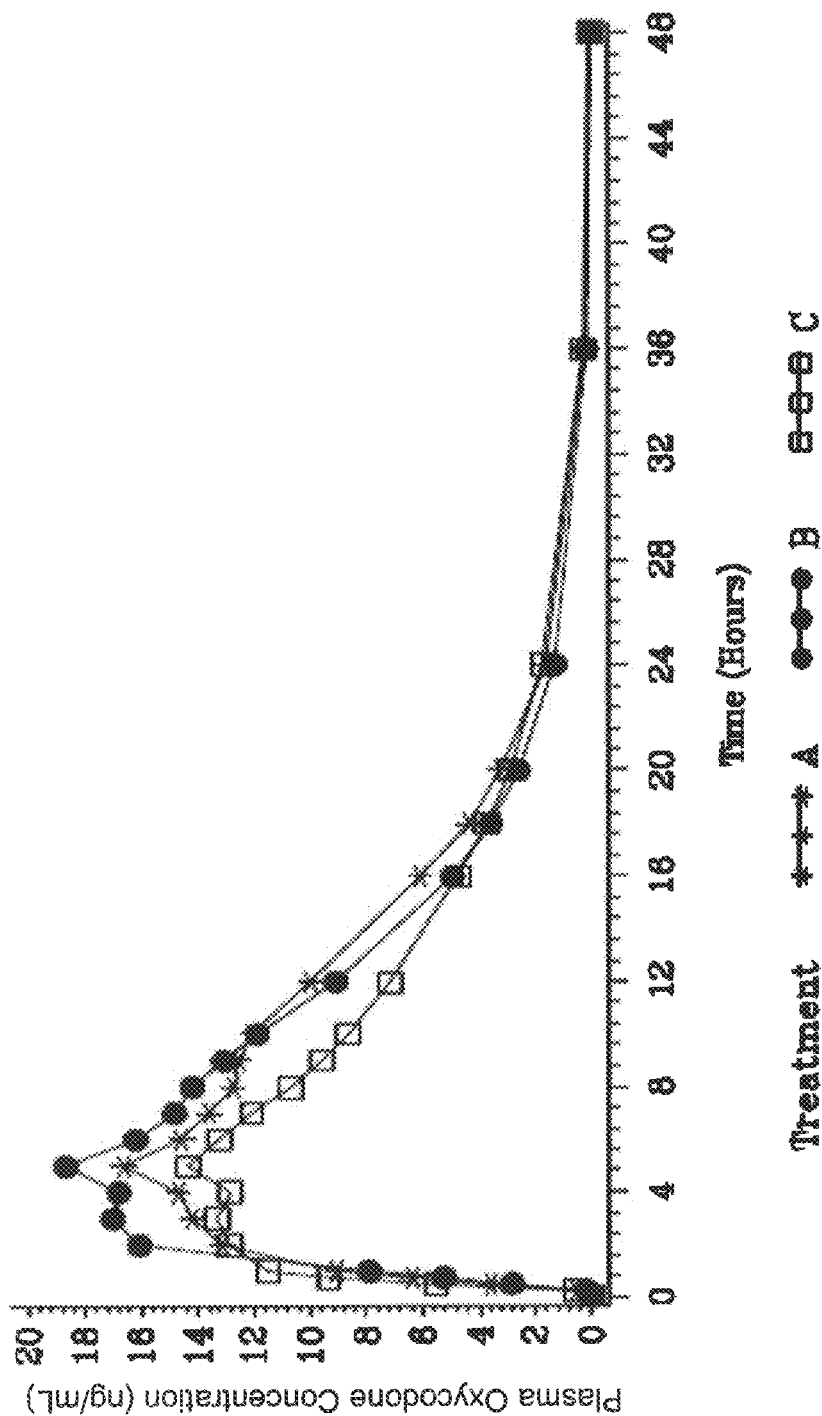


FIG. 19

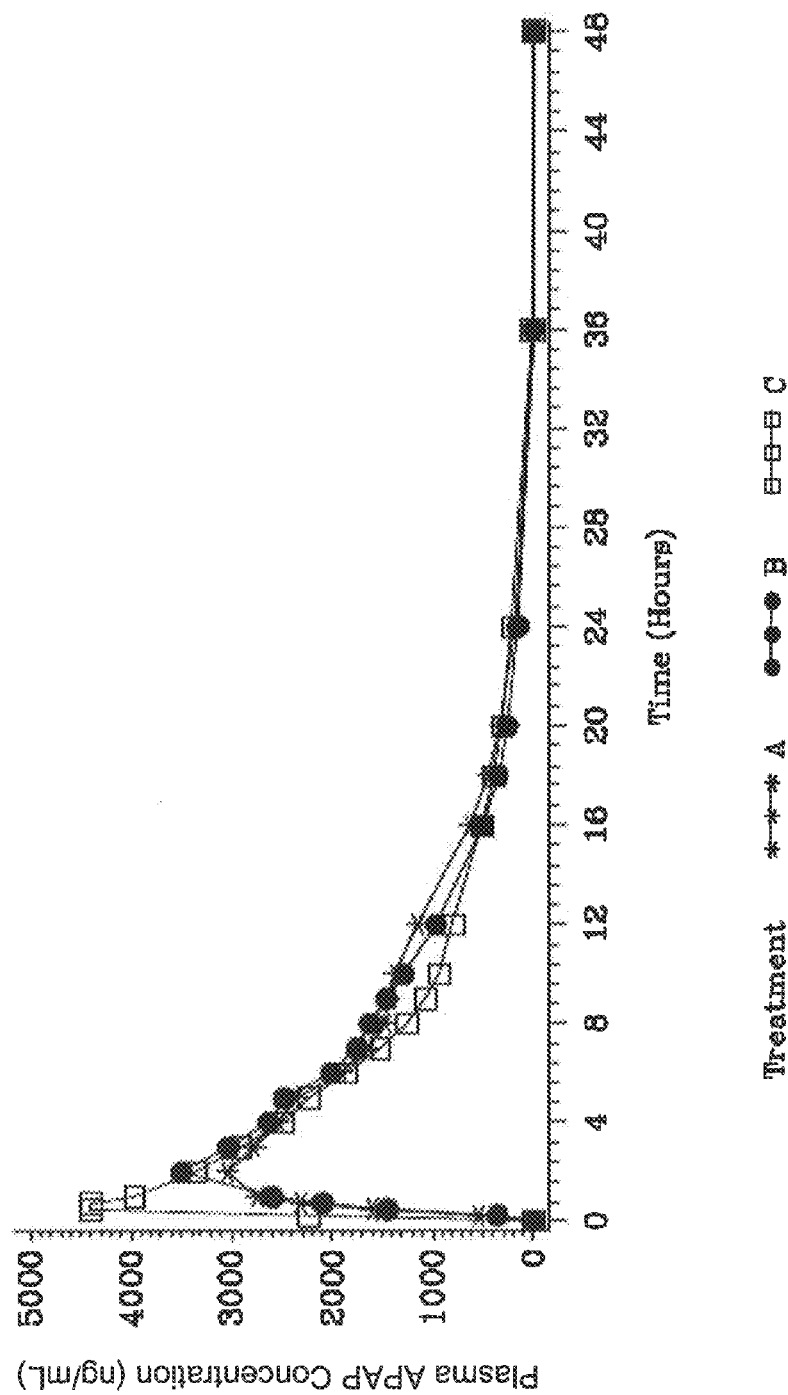


FIG. 20

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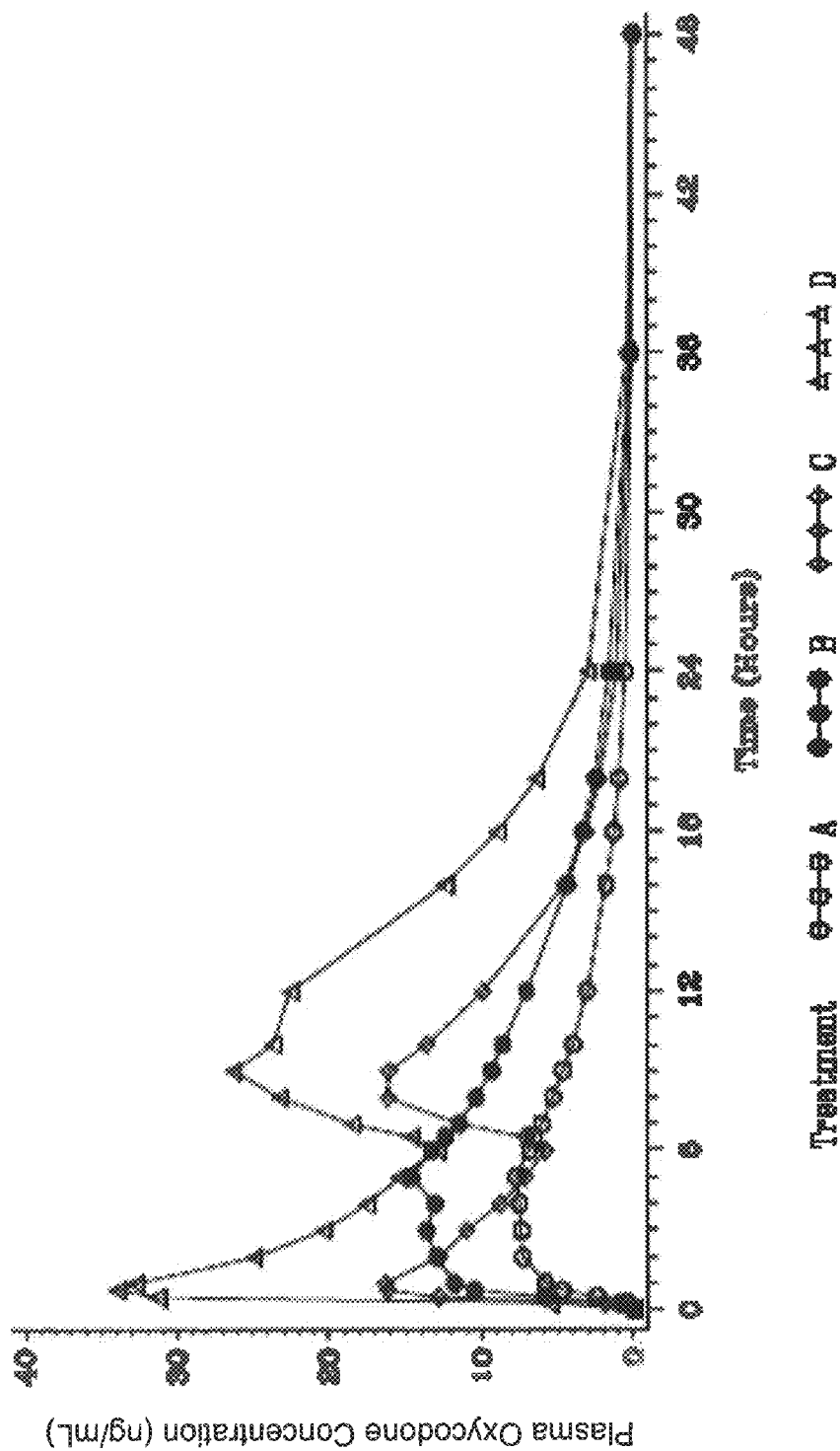


FIG. 21

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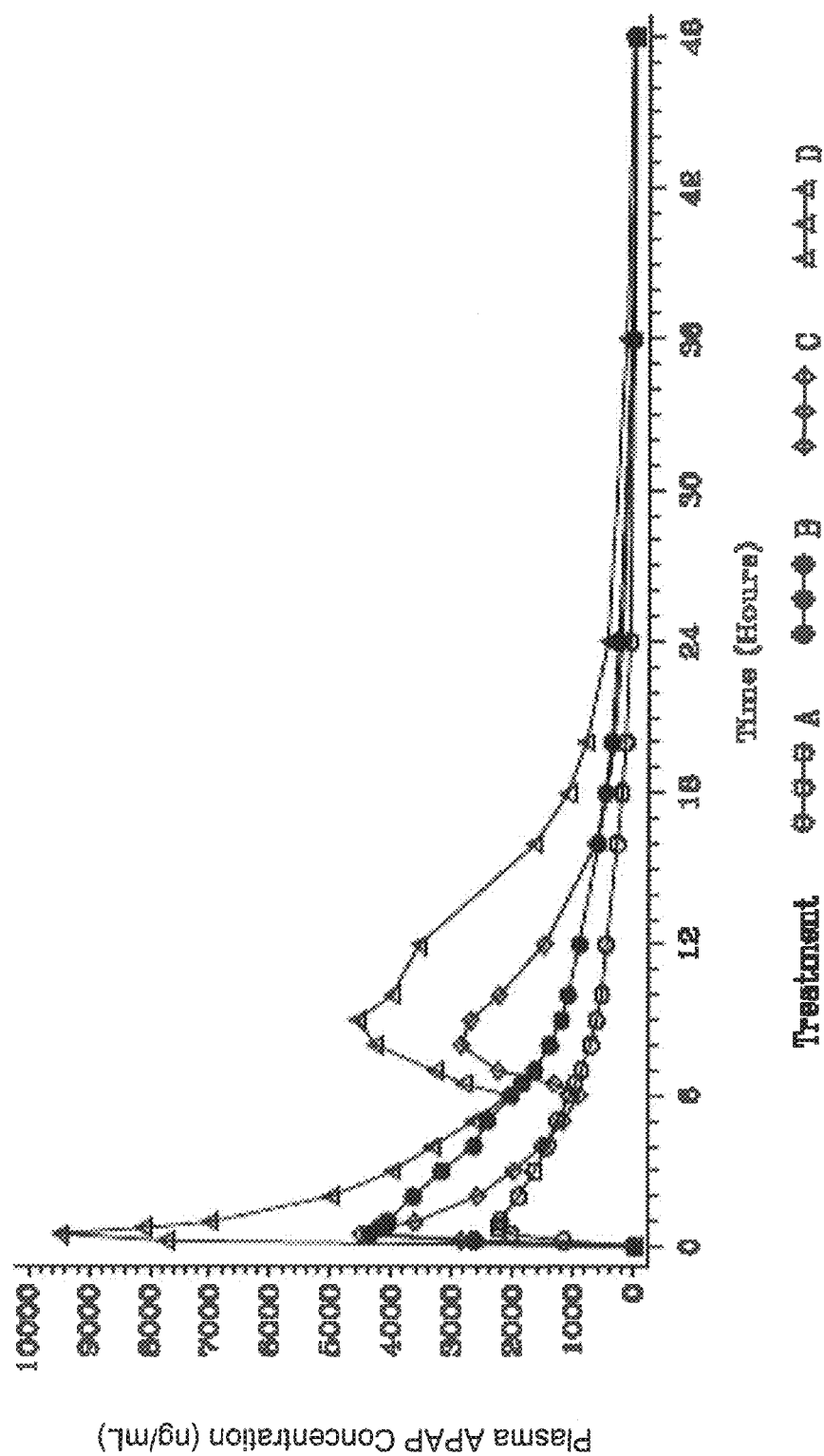


FIG. 22

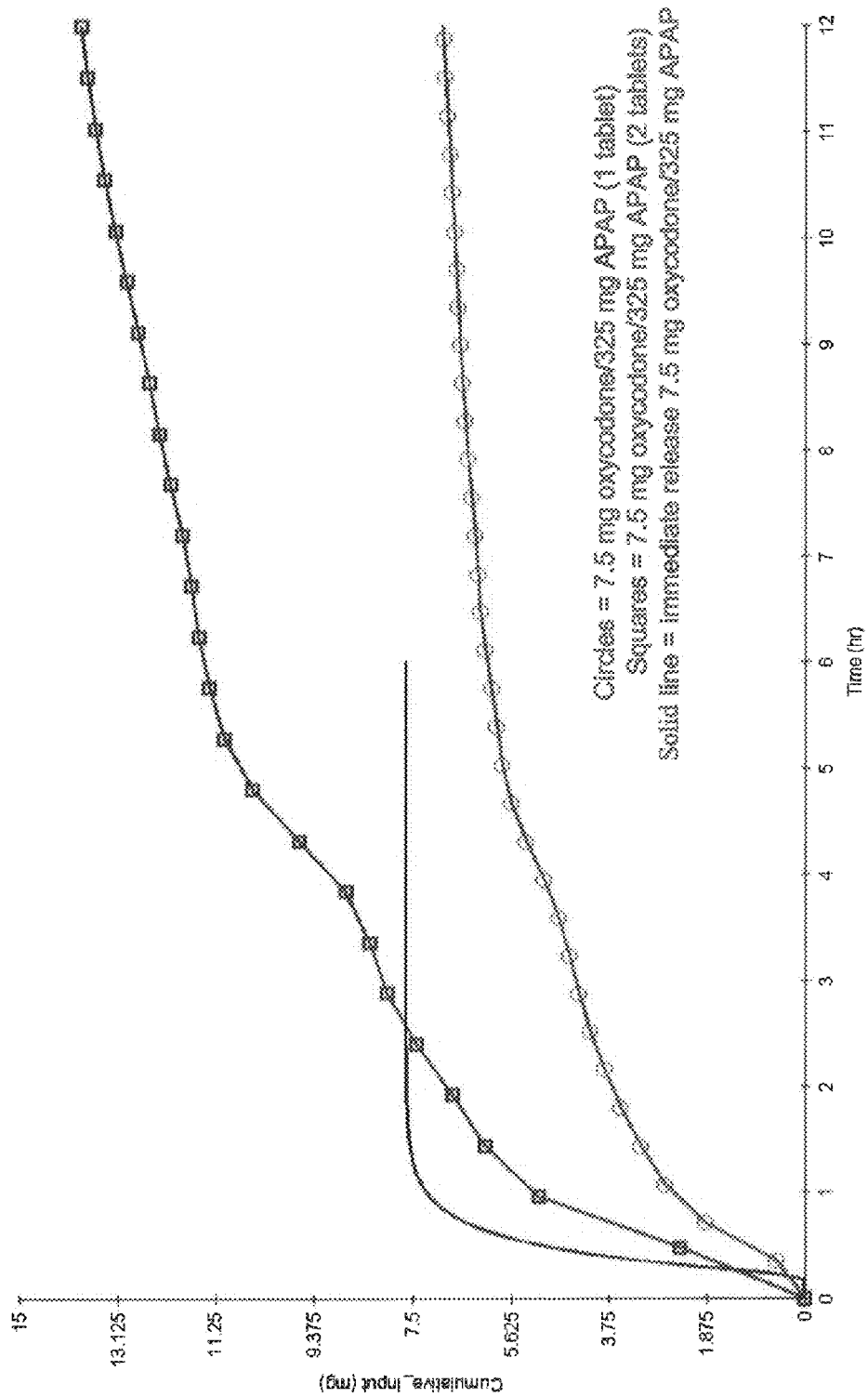


FIG. 23

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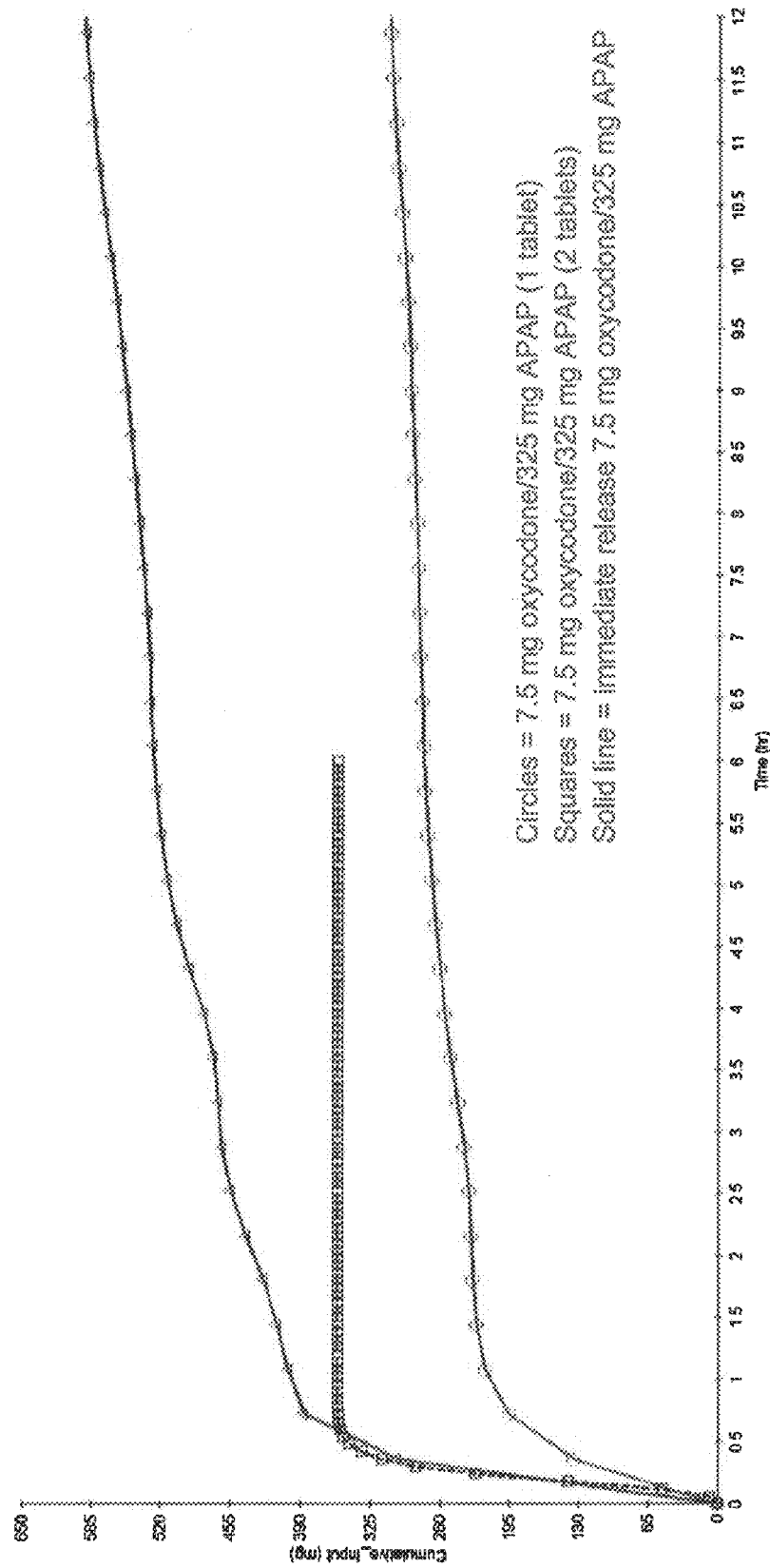


FIG. 24

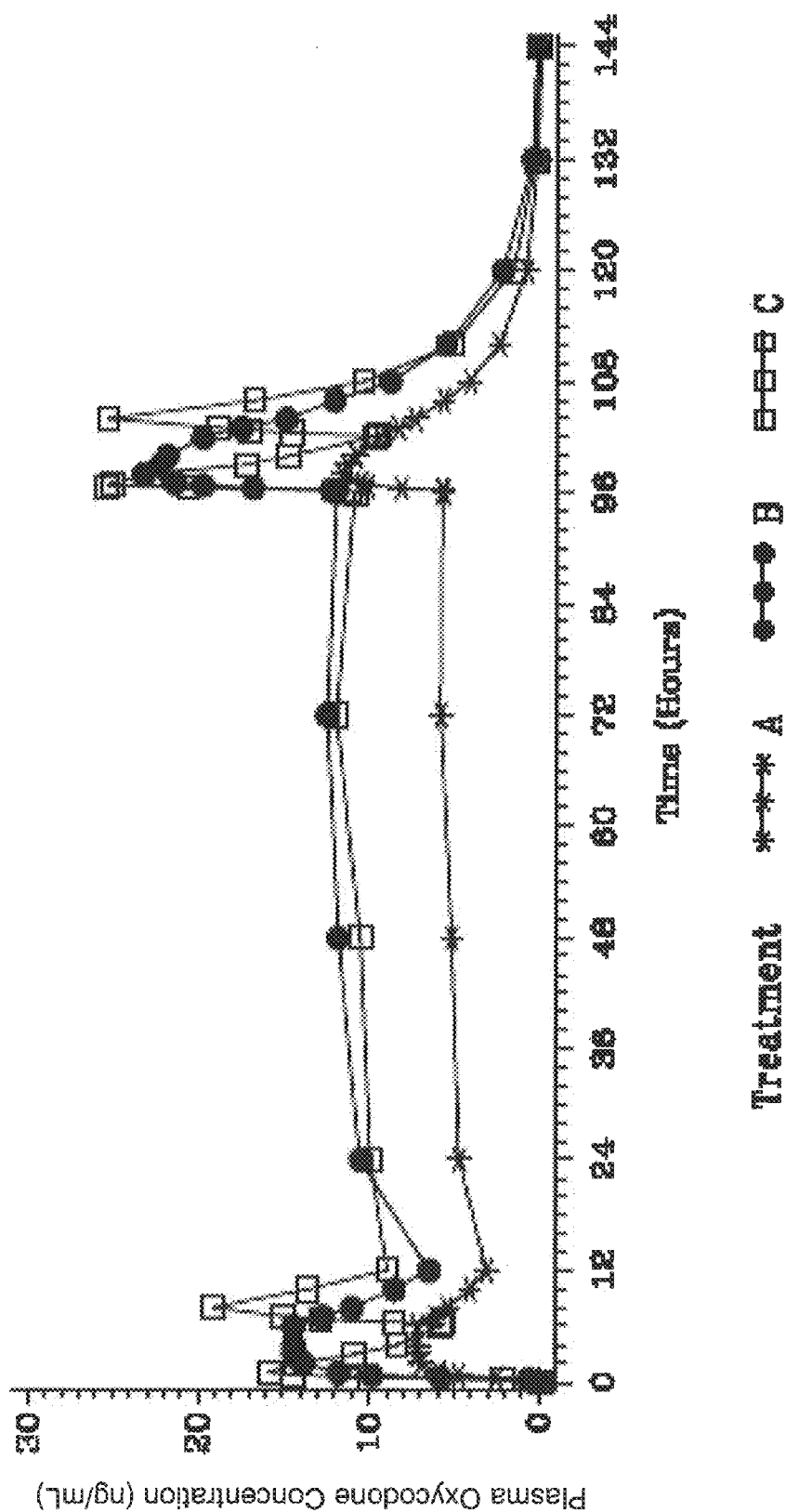


FIG. 25

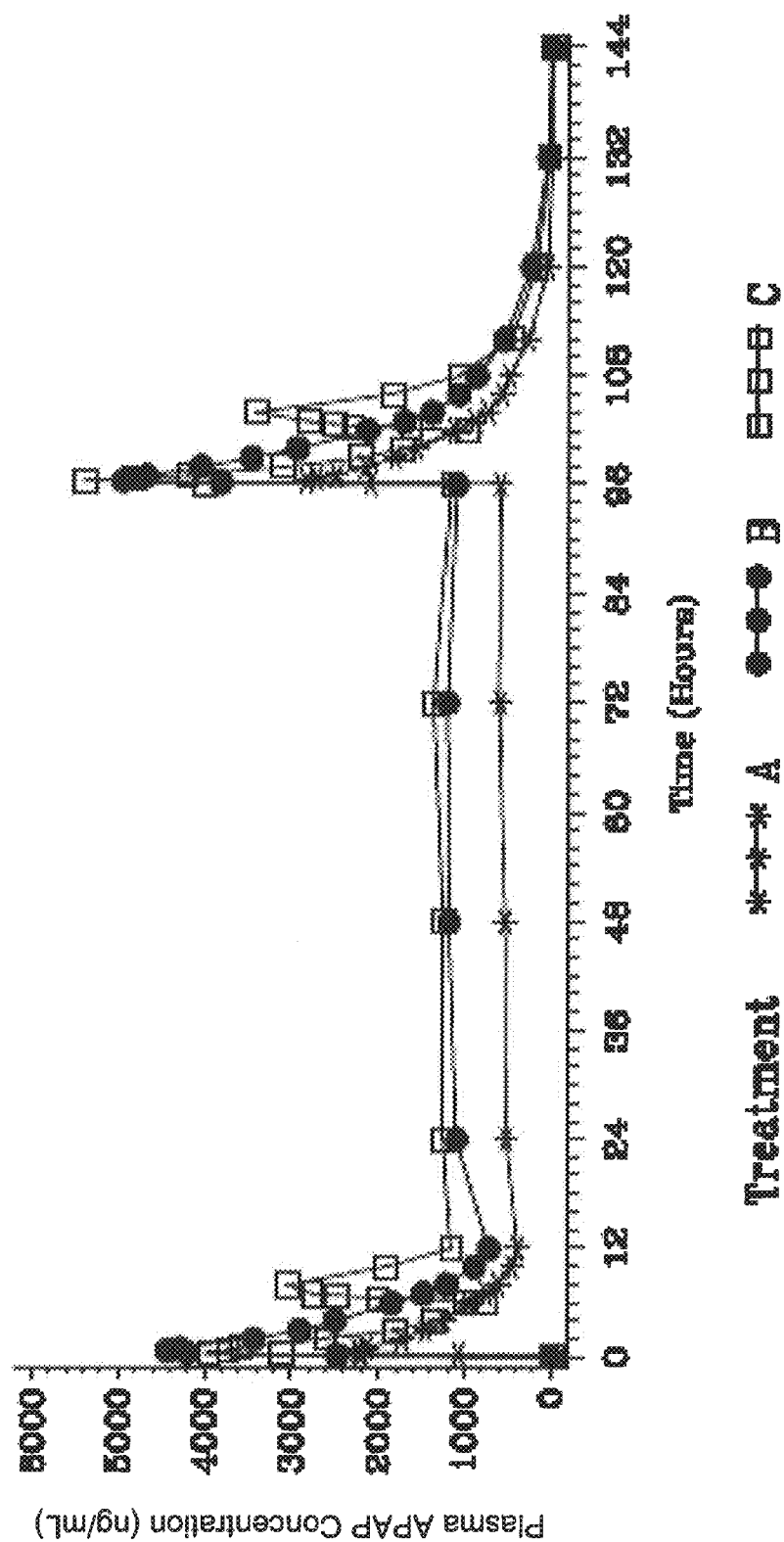


FIG. 26

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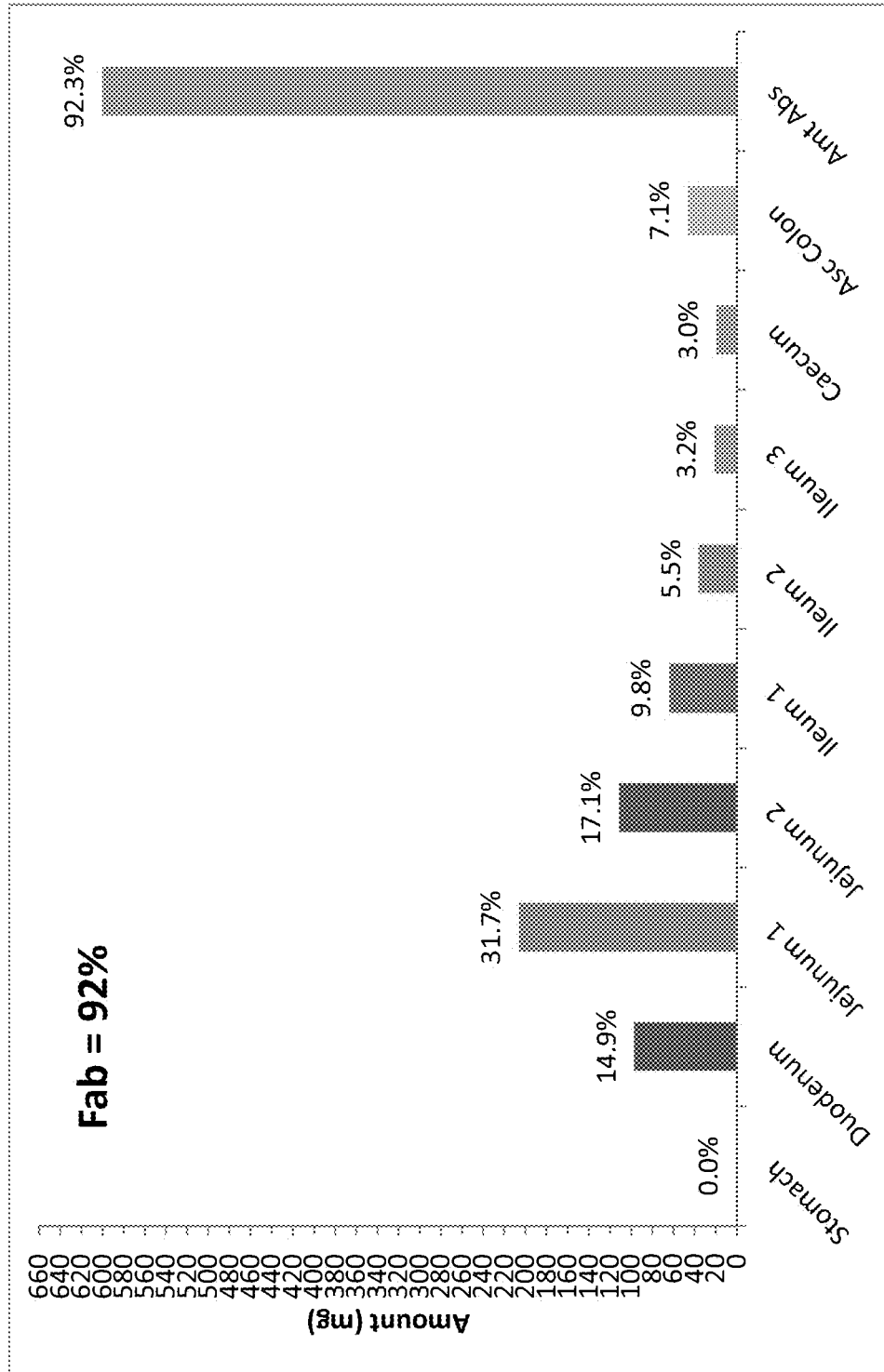
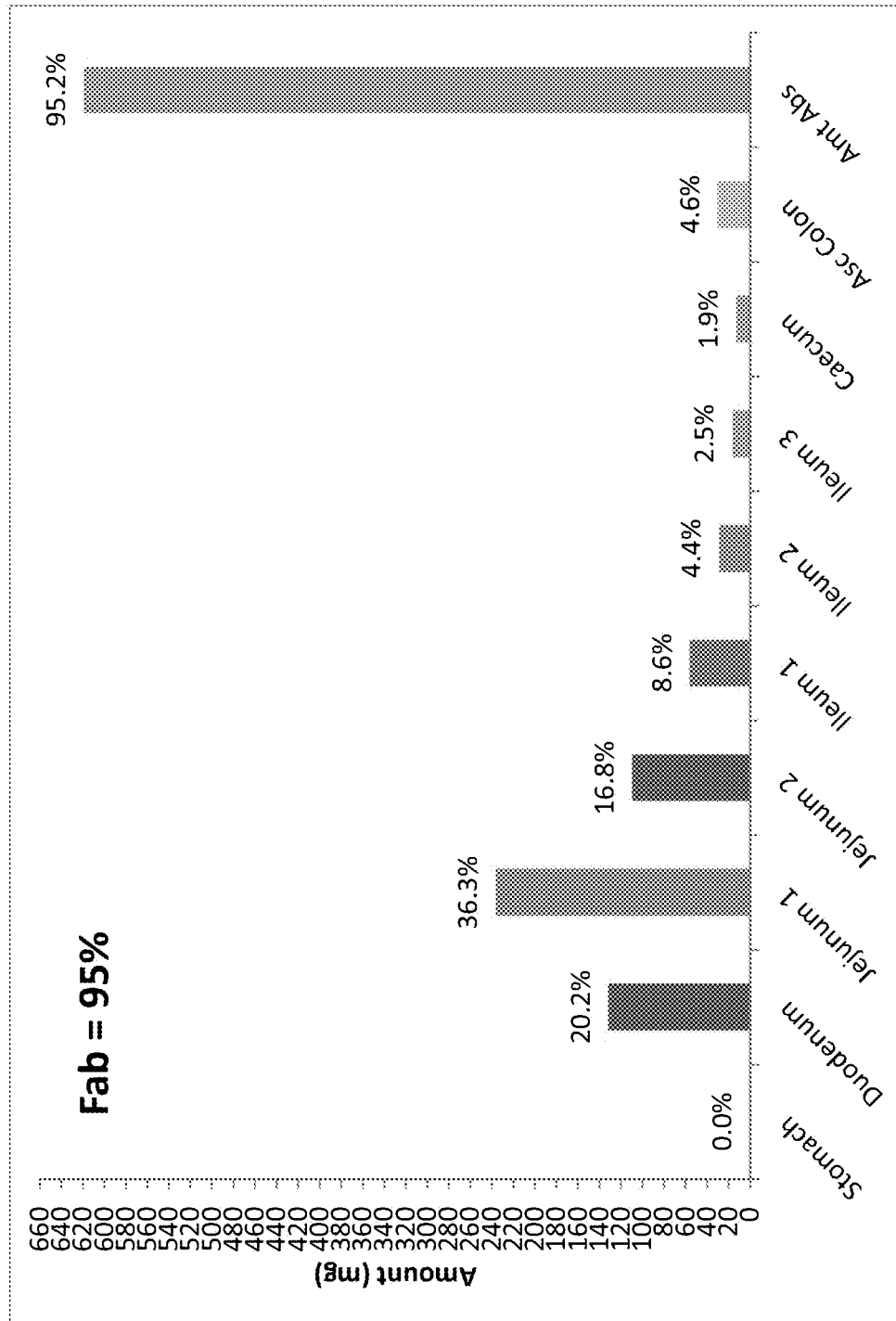
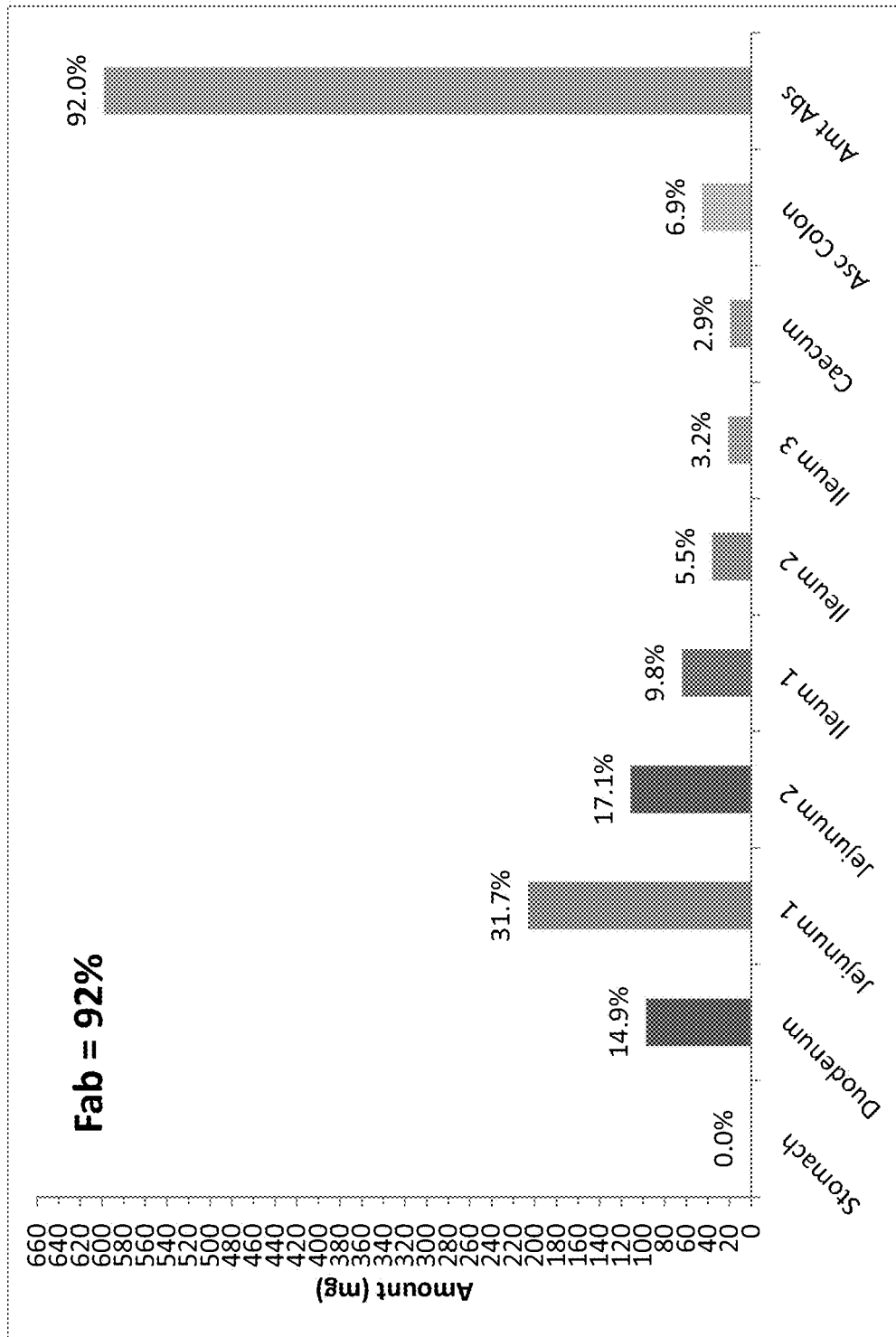


FIG. 27A

**FIG. 27B**

**FIG. 27C**

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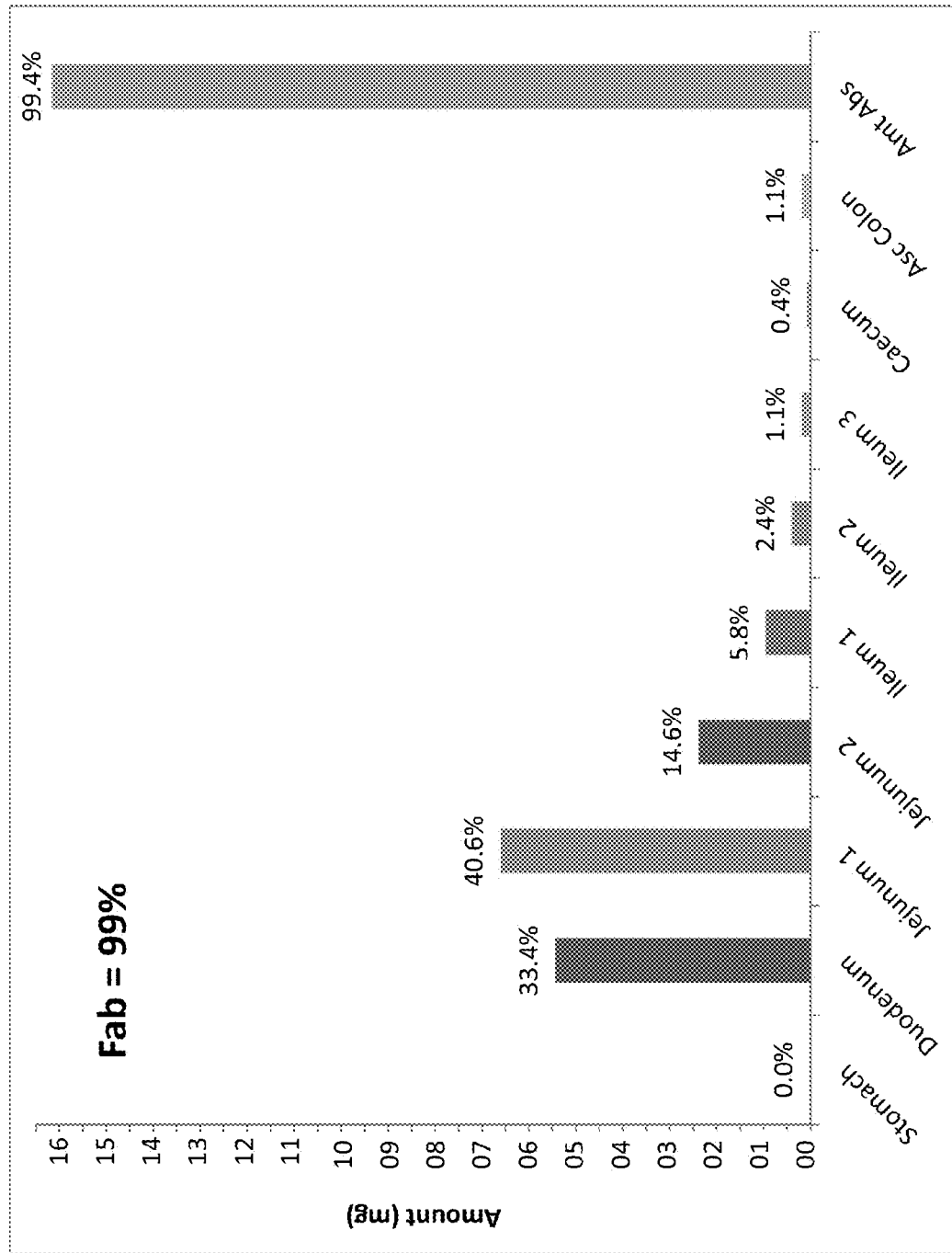
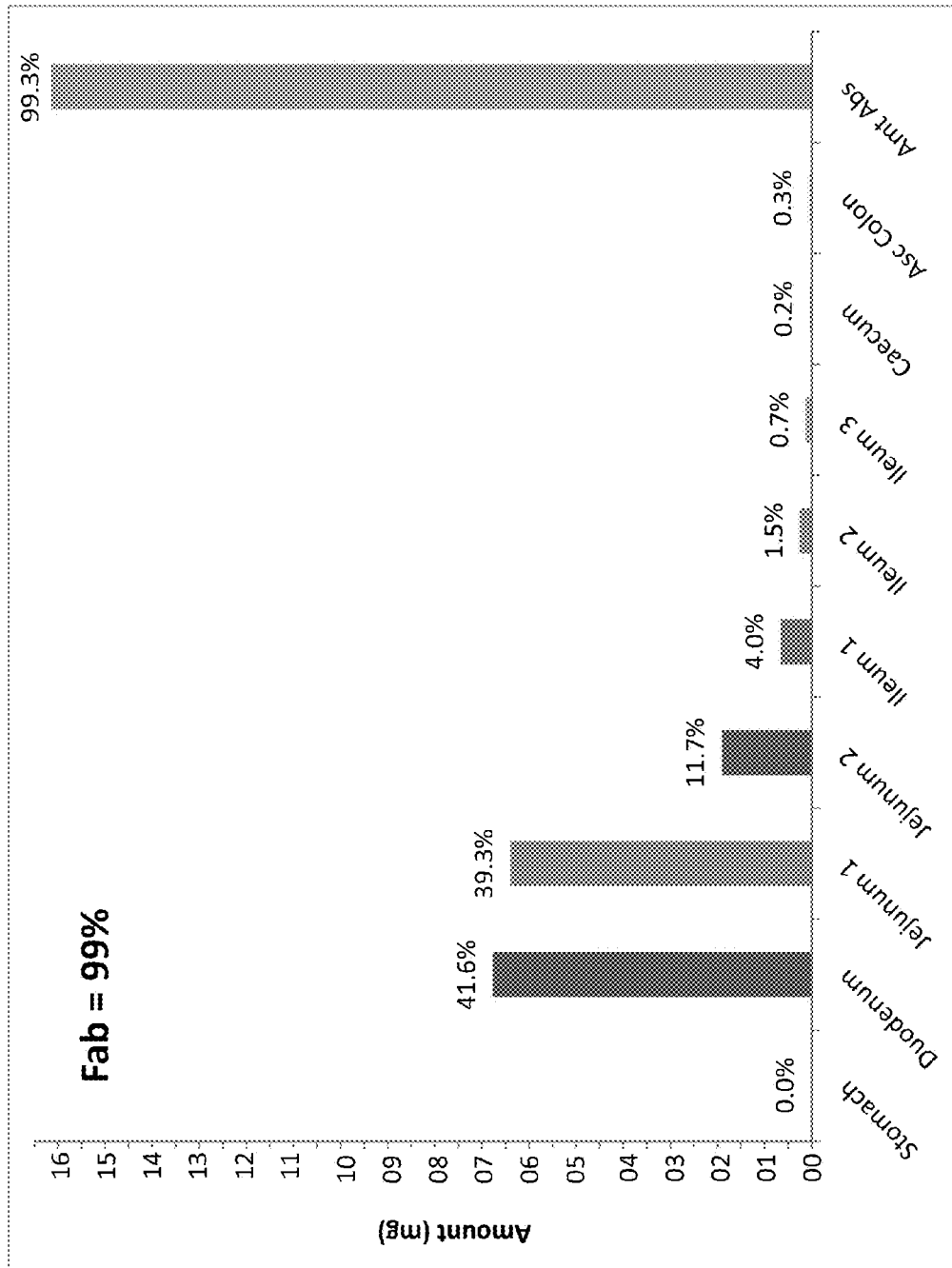


FIG. 28A

**FIG. 28B**

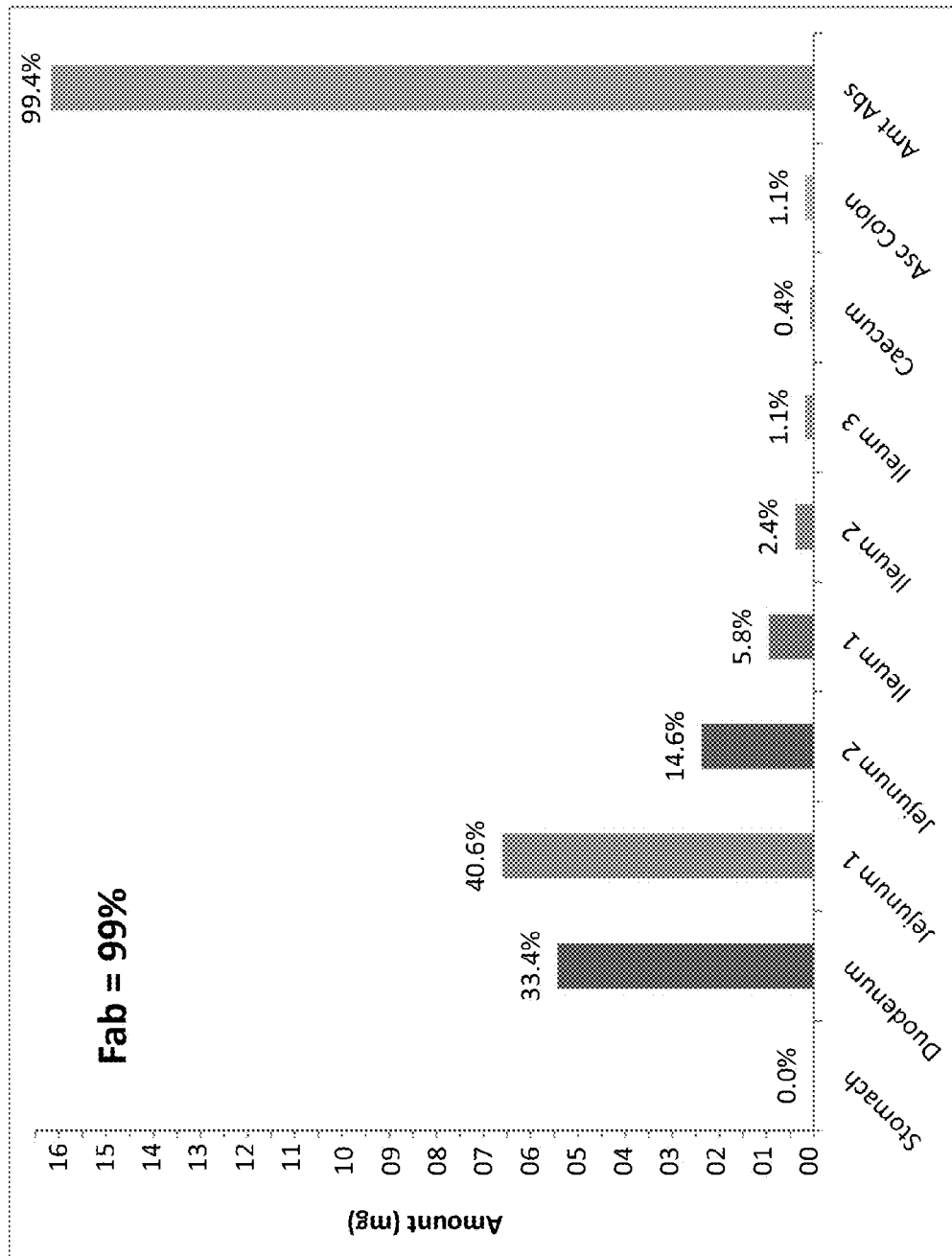


FIG. 28C

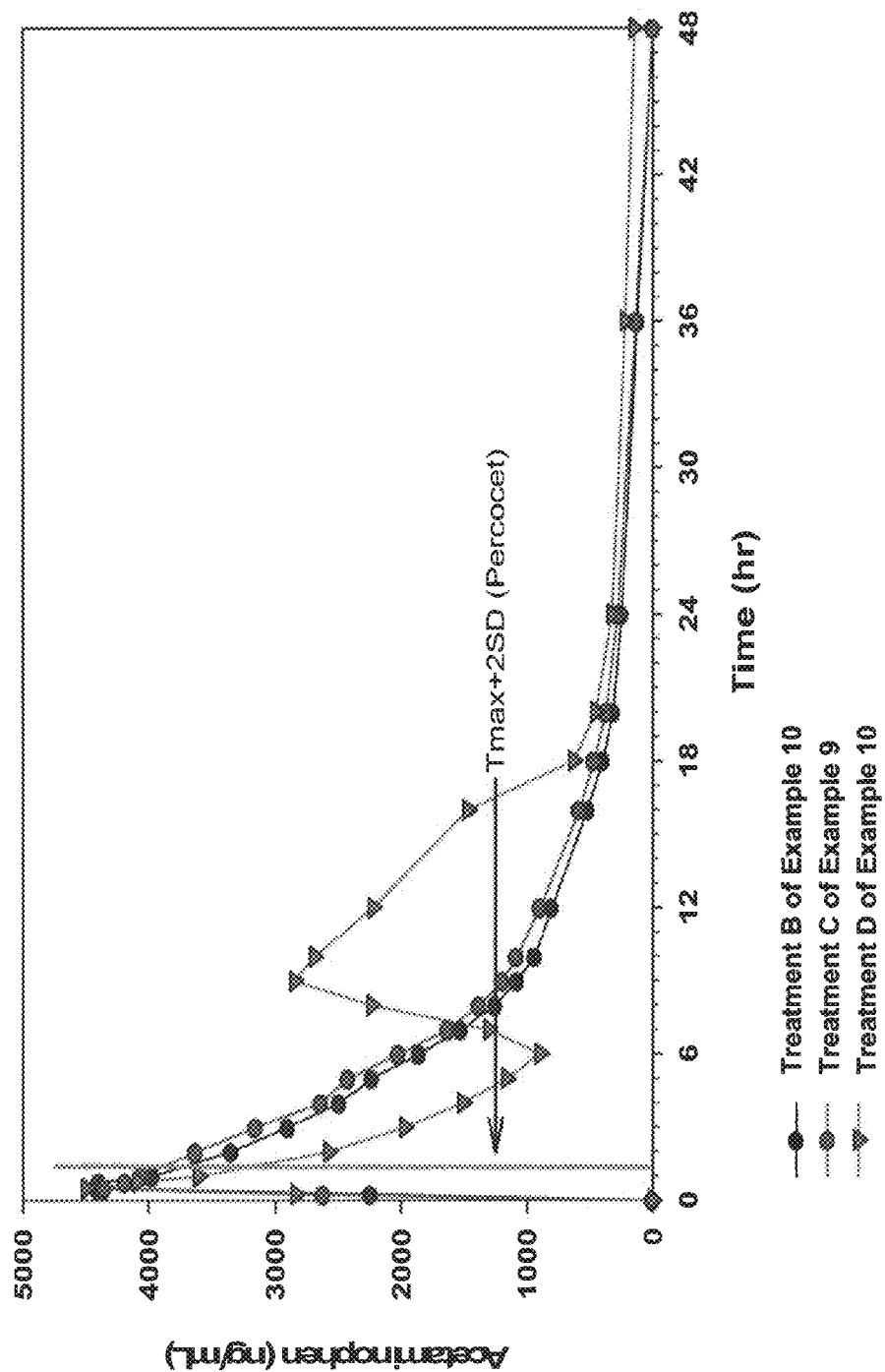


FIG. 29A

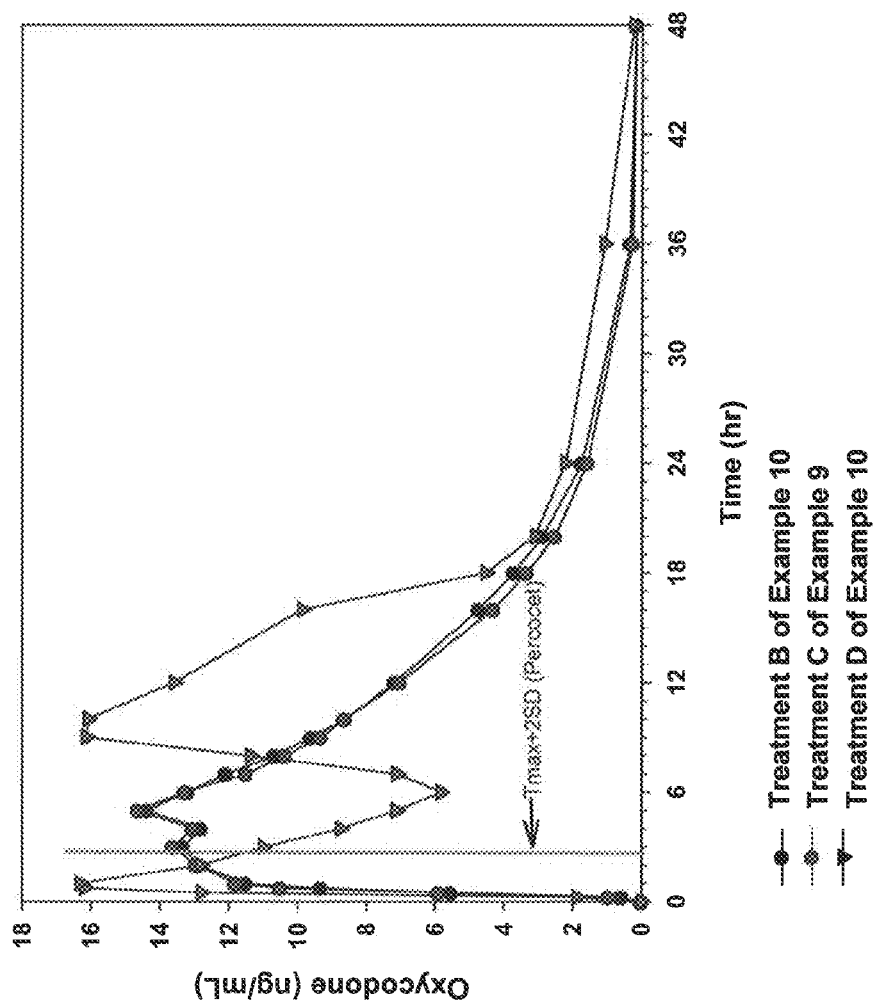


FIG. 29B

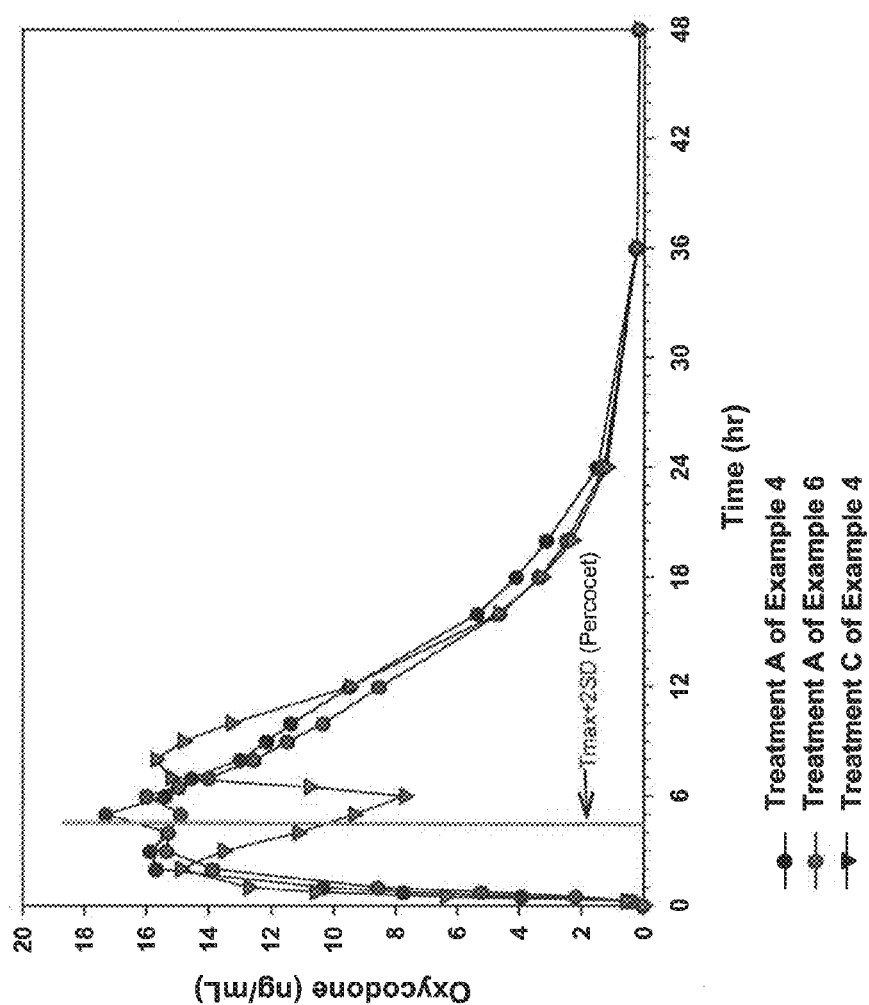


FIG. 30A

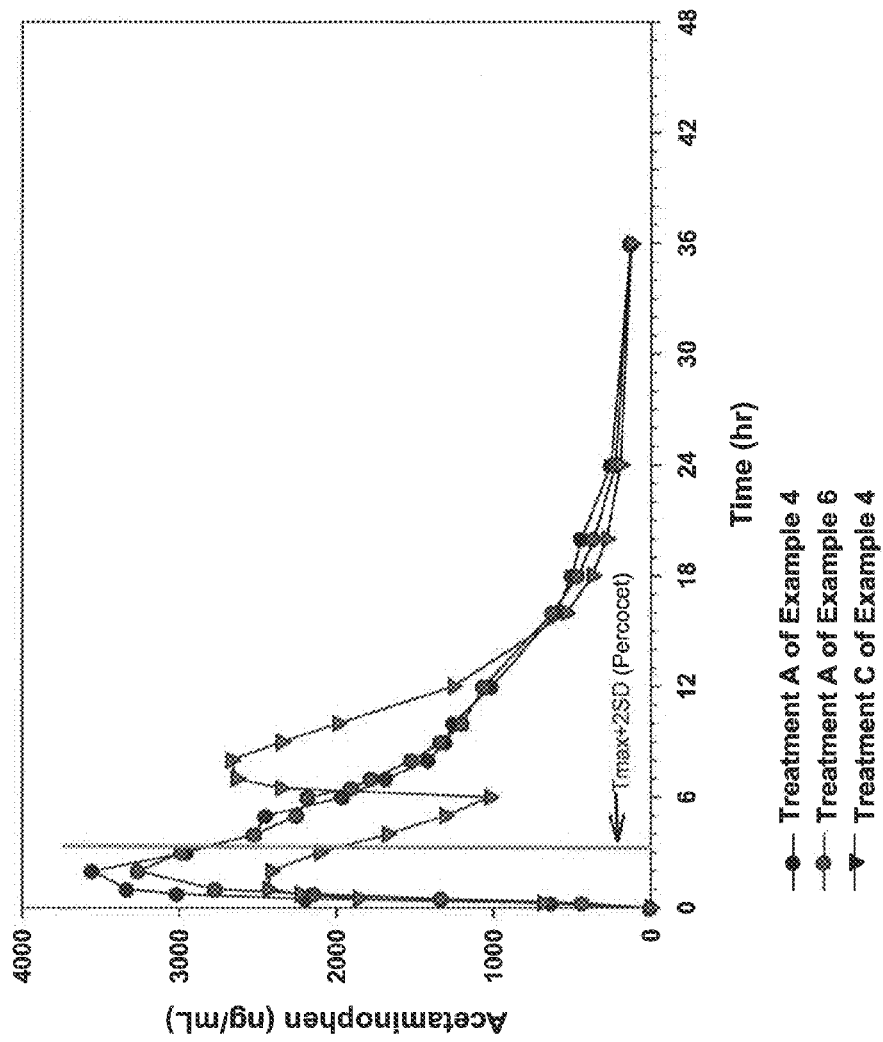


FIG. 30B

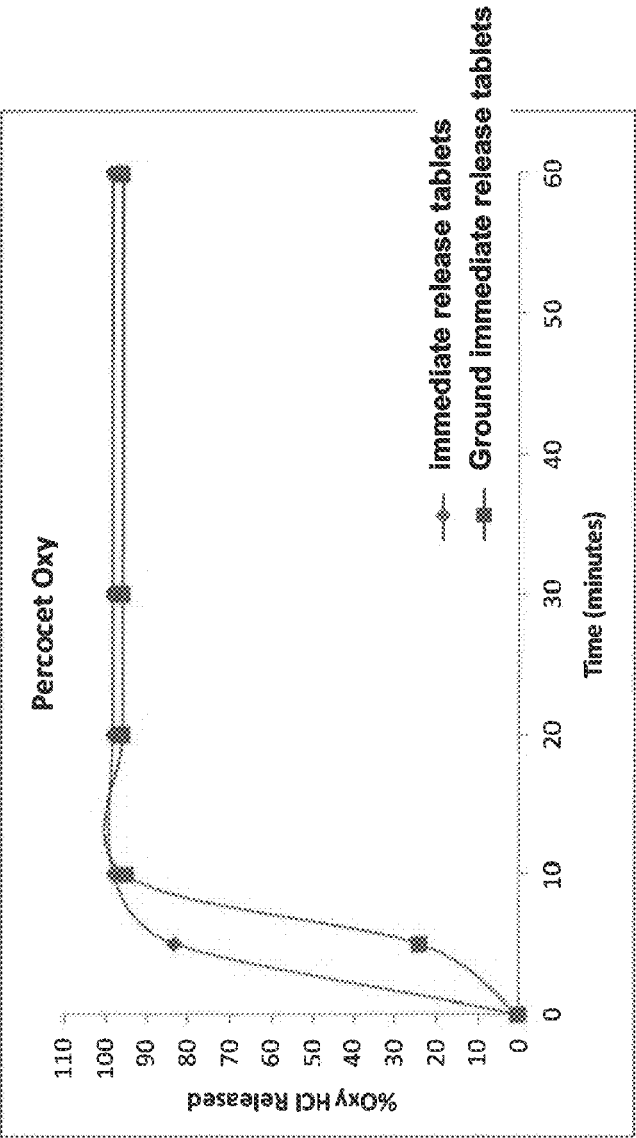


FIG. 31

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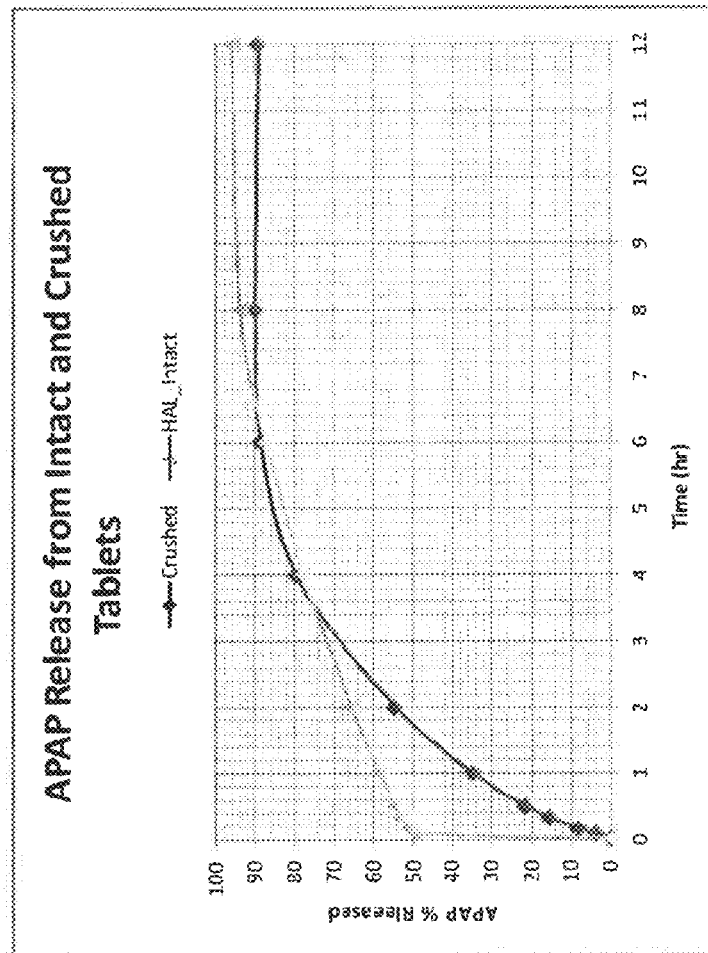


FIG. 32A

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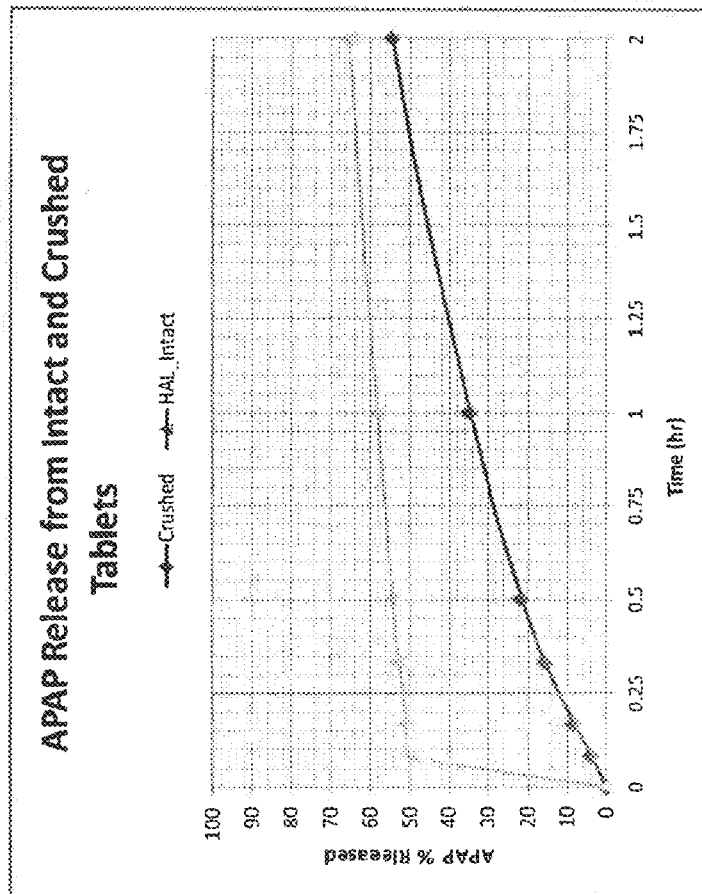


FIG. 32B

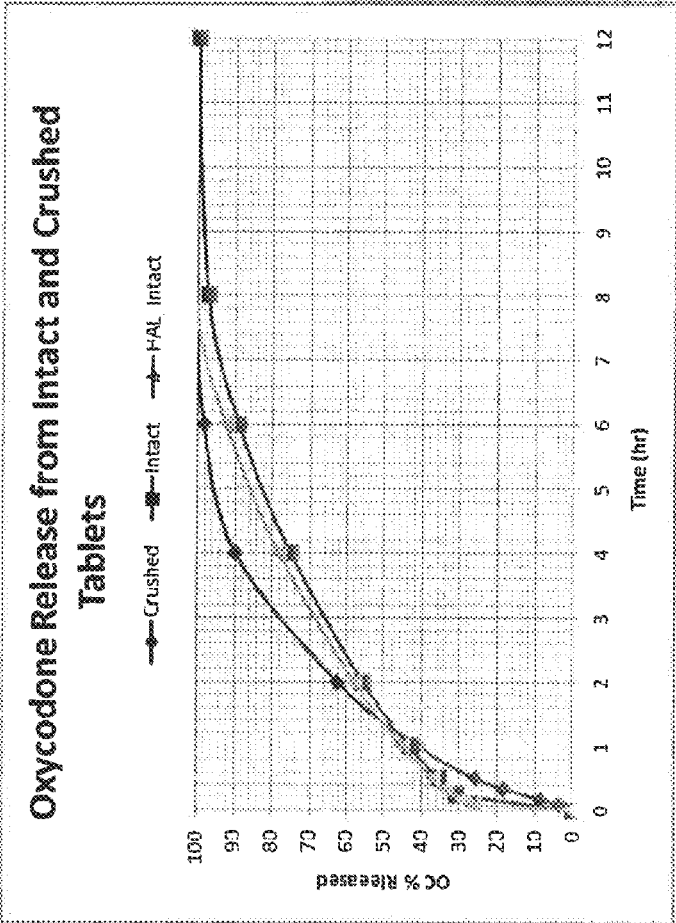


FIG. 33A

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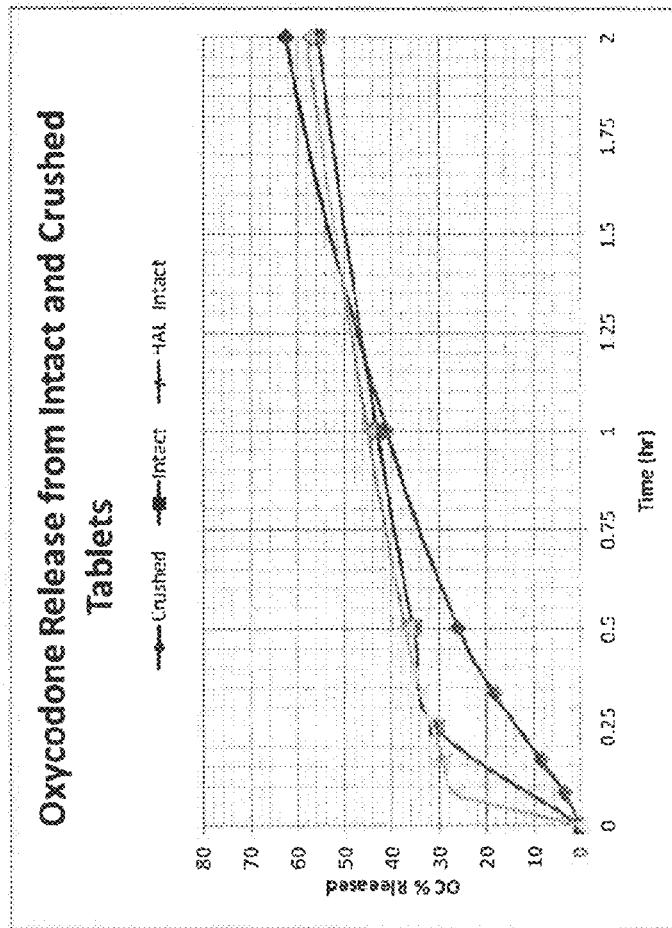


FIG. 33B

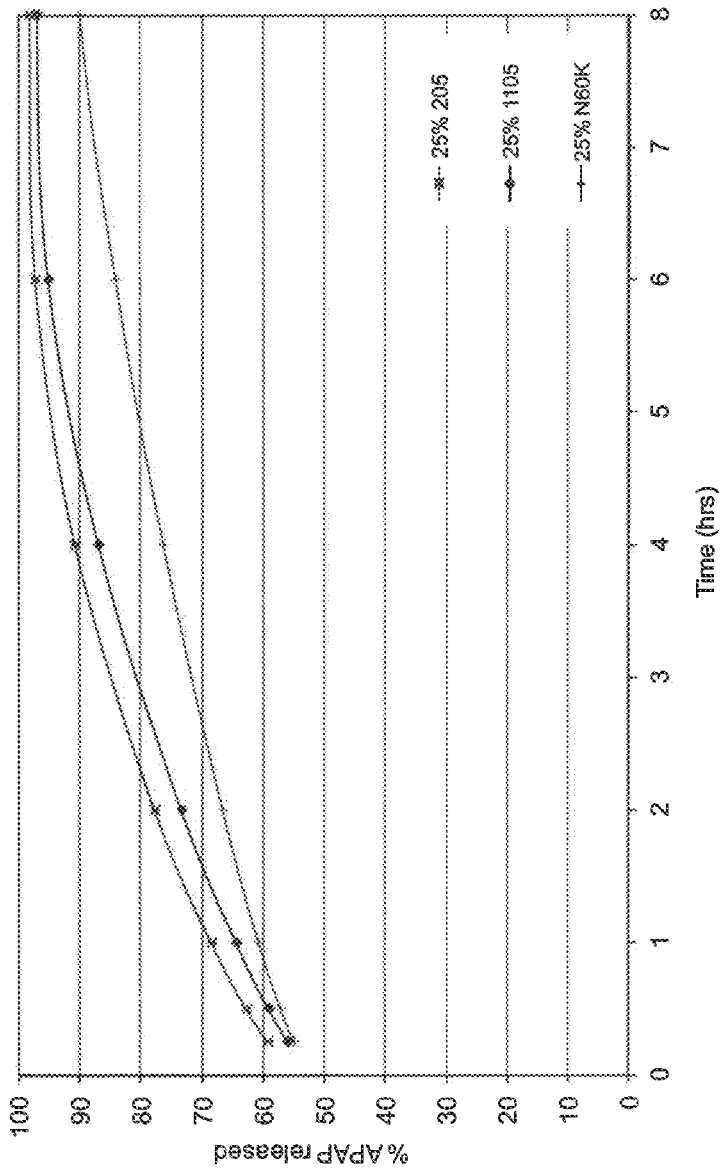


FIG. 34

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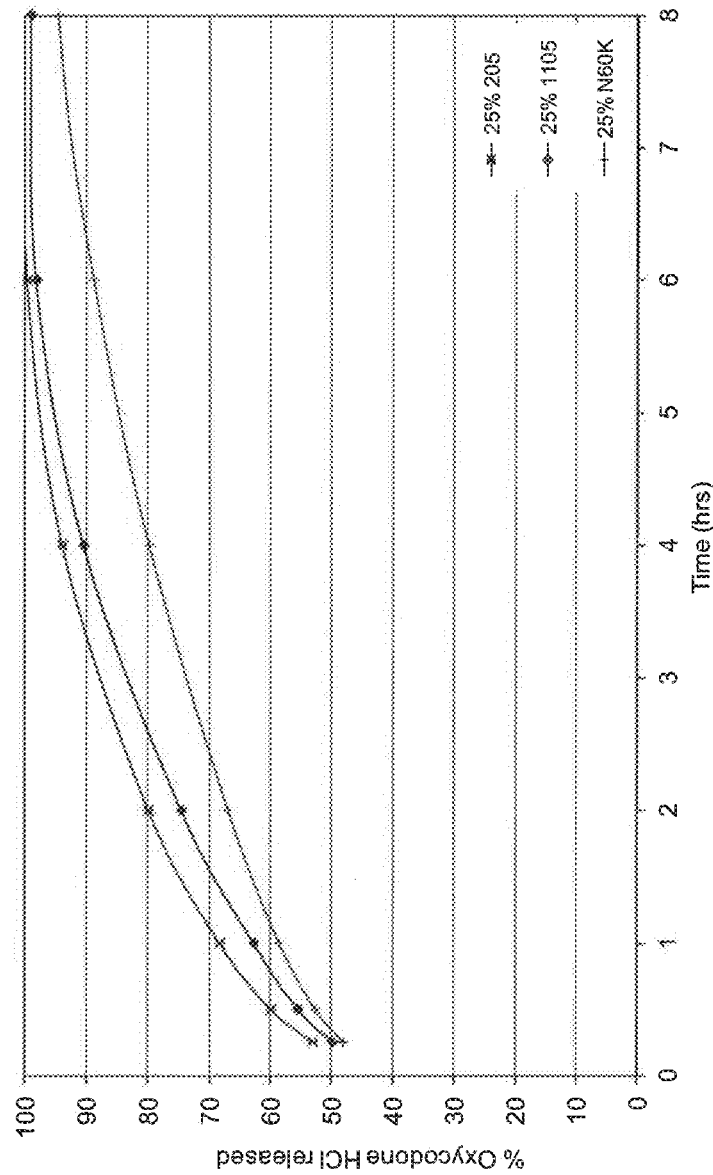


FIG. 35

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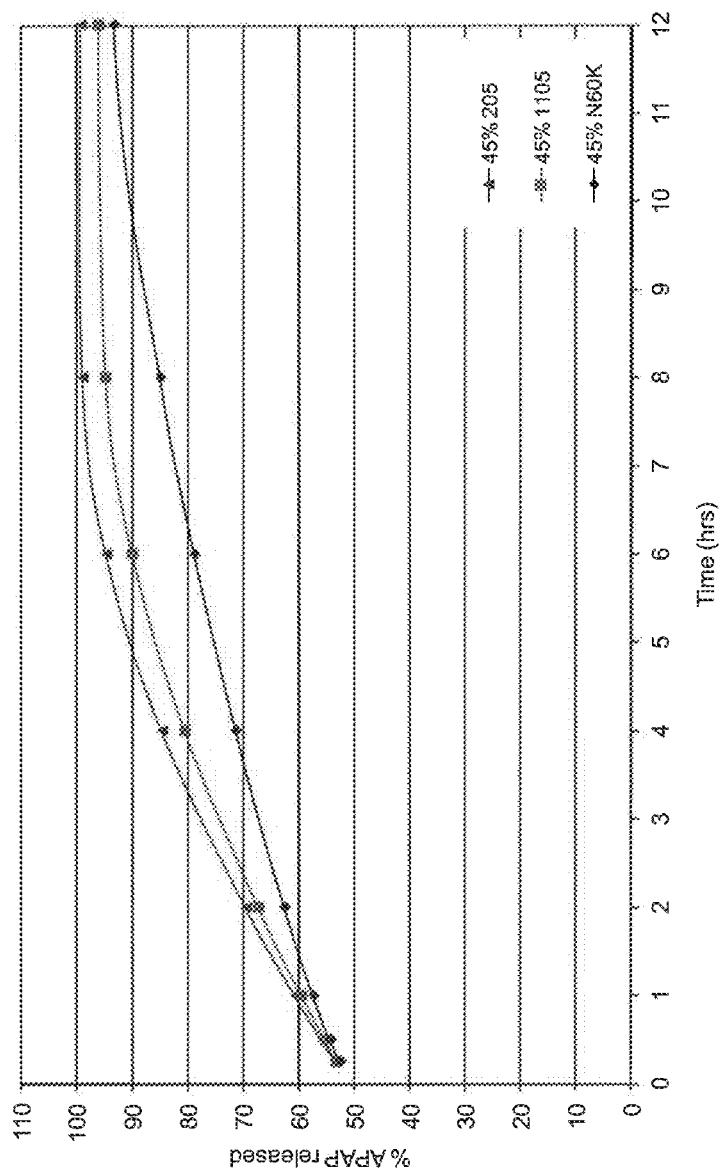


FIG. 36

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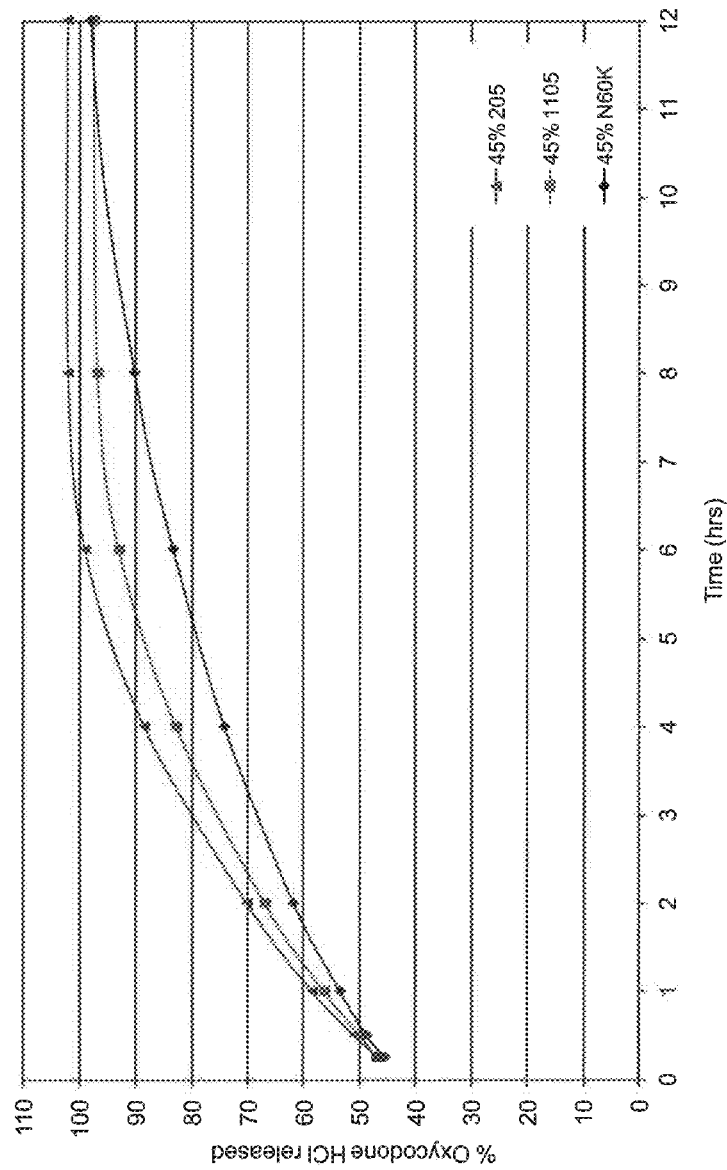


FIG. 37

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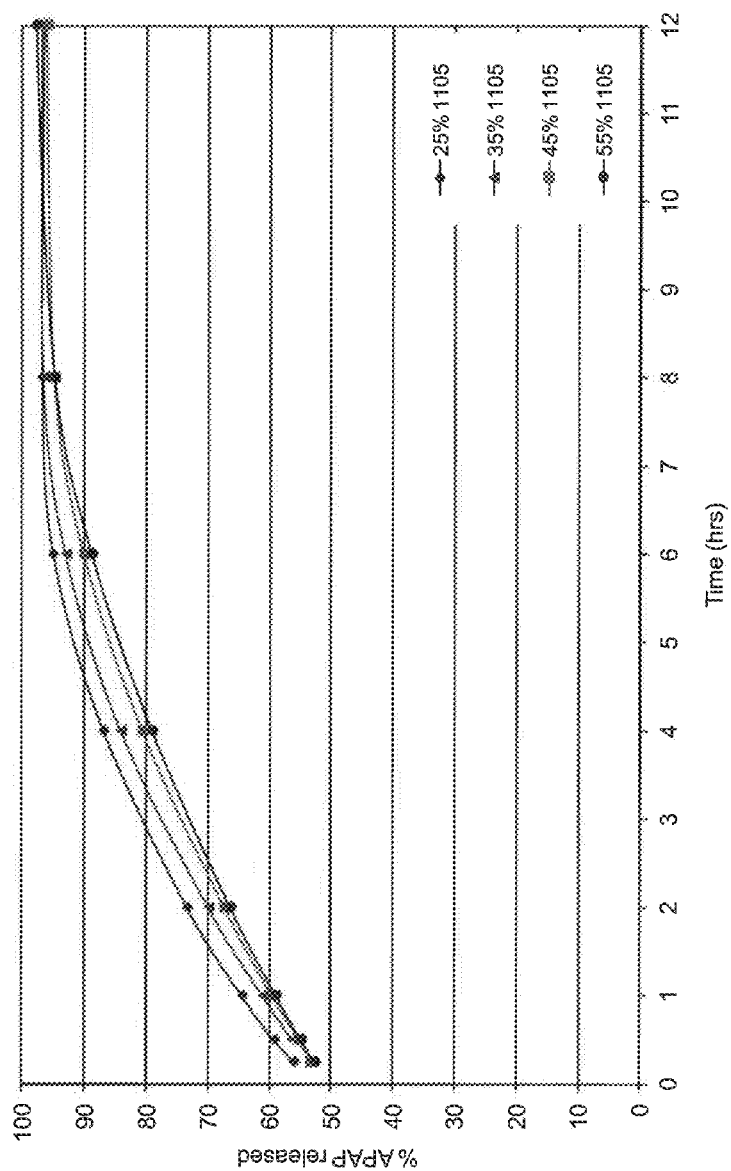


FIG. 38

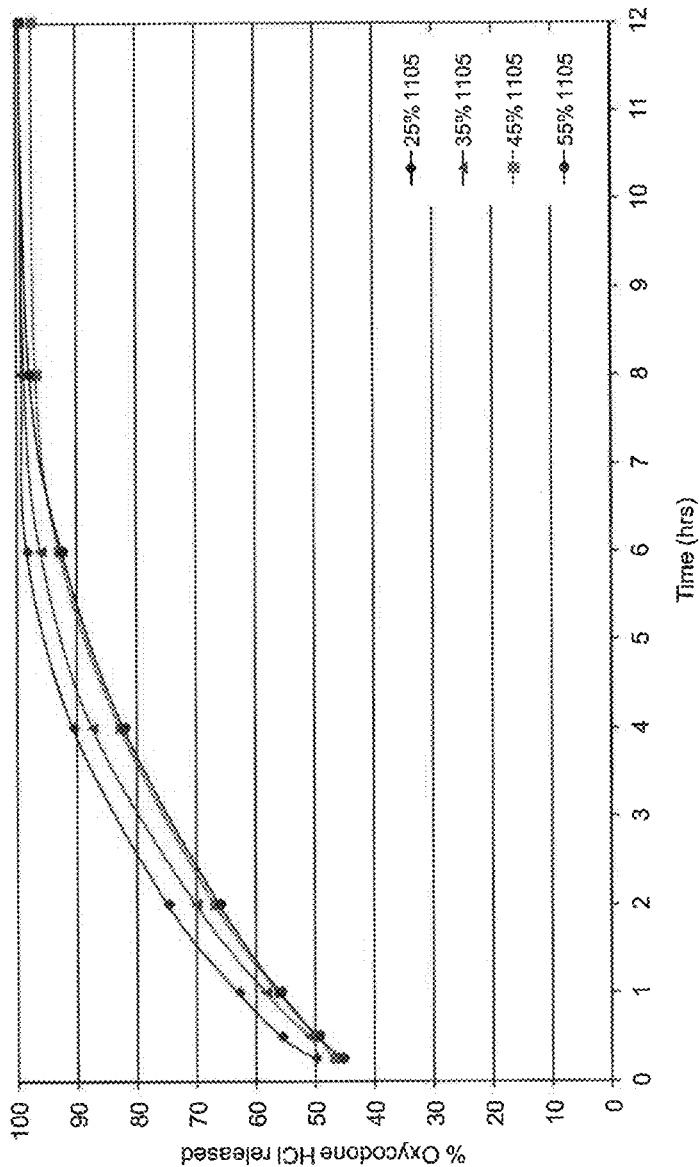


FIG. 39

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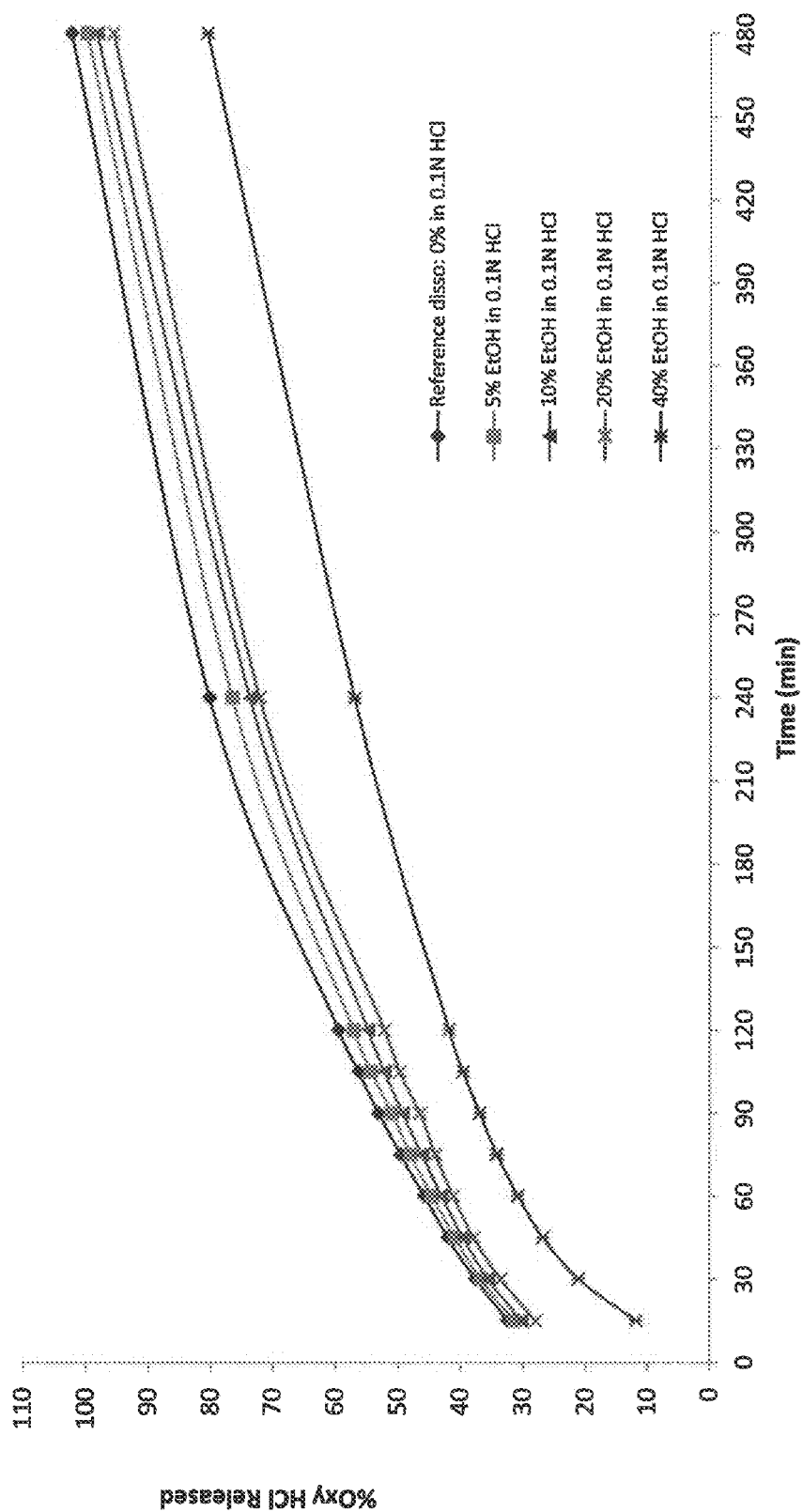


FIG. 40

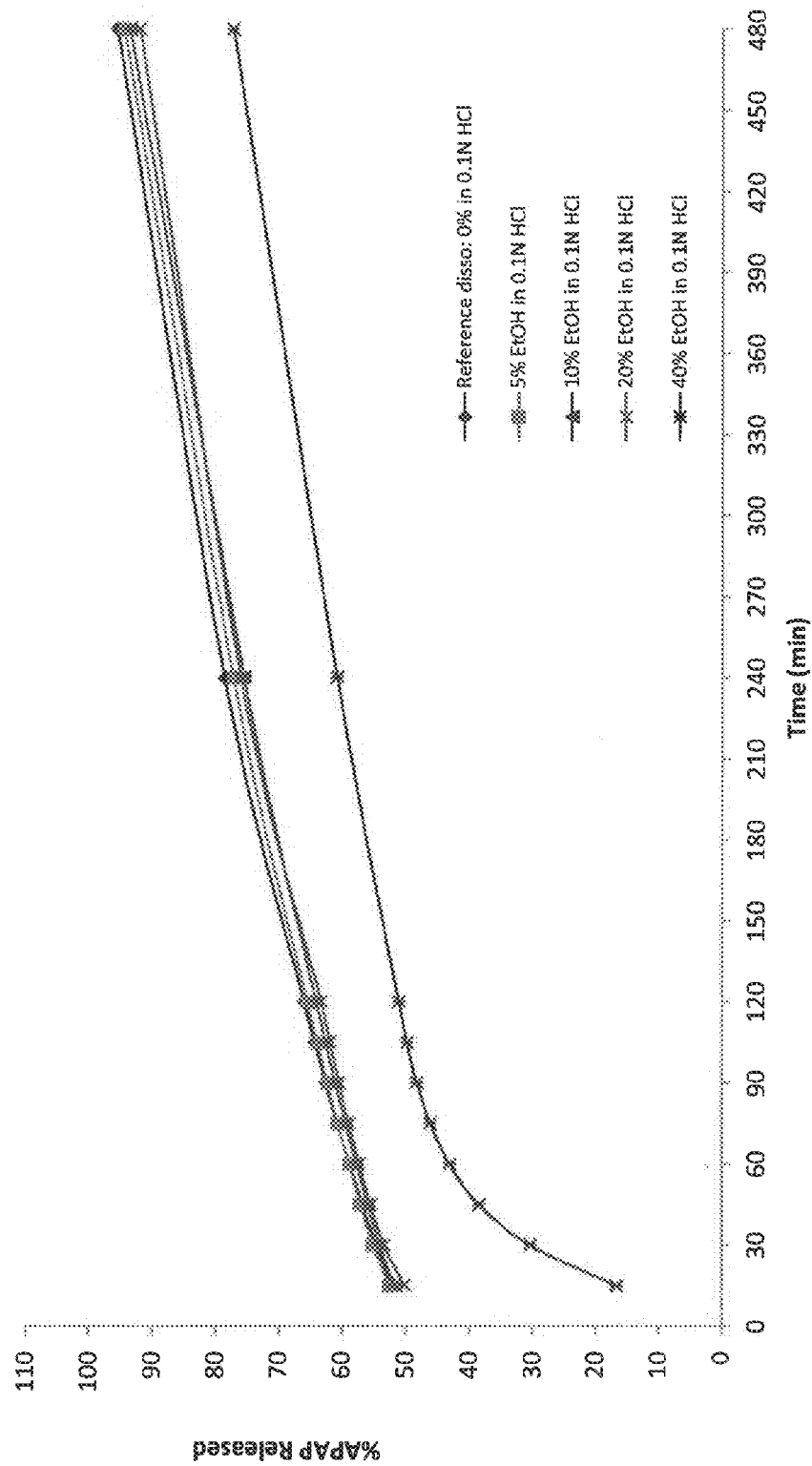


FIG. 41

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**COMBINATION COMPOSITION
COMPRISING OXYCODONE AND
ACETAMINOPHEN FOR RAPID ONSET AND
EXTENDED DURATION OF ANALGESIA**

RELATED CASES

This application is a continuation of U.S. application Ser. No. 13/473,563 filed on May 16, 2012 which claims priority to U.S. Provisional Application No. 61/487,047 filed on May 17, 2011, U.S. Provisional Application No. 61/537,527 filed on Sep. 21, 2011, and U.S. Provisional Application No. 61/606,850 filed on Mar. 5, 2012 which are incorporated herein by reference in their entirety to the full extent permitted by law.

FIELD OF THE INVENTION

The present disclosure relates to an extended release pharmaceutical composition comprising oxycodone and acetaminophen that provides a rapid onset of analgesia, followed by an extended duration of analgesia of about 12 hours.

BACKGROUND OF THE INVENTION

Oral drug administration remains the route of choice for the majority of clinical applications. Modified release (MR) dosage forms that are administered once or twice daily offer advantages over their immediate release (IR) counterparts because they reduce the magnitude of peaks and troughs of drug plasma concentration, provide longer dosing intervals, sustained analgesic effect, and increased patient compliance. These modified release formulations may be referred to as controlled release (CR), sustained release (SR) and/or extended release (ER) etc. For certain types of patients, such as those suffering from pain, these MR products may permit the patient to sleep through the night without having to wake up during the night to take the next dose. Thus, it can significantly increase the quality of life for such patients. Both IR and MR products for pain are widely available in the market. Examples of IR products include those containing NSAIDs, opioids, profens, COX II inhibitors and aspirin (Tylenol, Advil, Celebrex, Vioxx, Aleve, Voltaren). Examples of MR products include those containing NSAIDs and opioids (Tylenol SR, Oxycontin).

Researchers have also combined various classes of pain drugs to provide better analgesia to patients. For example, a combination of acetaminophen-oxycodone hydrochloride is commercially available as Percocet and acetaminophen-hydrocodone bitartrate as Vicodin. In randomized controlled trials, it was shown that the combination product Percocet was statistically superior to MR oxycodone in various outcome measures of pain relief. Other combination products such as Acetaminophen-Hydrocodone and Acetaminophen-Tramadol are either available or described in the literature. It is postulated that the combination of two analgesic drugs with complementary mechanisms of action results in enhanced analgesia due to an additive effect, an "opioid-sparing" effect, and an improved side effect and safety profile. The improved safety profile results from the use of reduced doses of two analgesics with different side-effects rather than an equieffective dose of a single agent.

Acetaminophen is absorbed from the small intestine and primarily metabolized by conjugation, like glucuronidation and sulfation, in the liver to nontoxic, water-soluble compounds that are eliminated in the urine. When the maximum daily dose is exceeded over a prolonged period, metabolism

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by conjugation becomes saturated, and excess acetaminophen is oxidatively metabolized by cytochrome P450 (CYP) enzymes (e.g., CYP2E1, 1A2, 2A6, 3A4) to a reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). NAPQI is a reactive free radical with an extremely short half-life that is rapidly inactivated by conjugation with glutathione, which is acting as a sulfhydryl donor. Once the pool of available glutathione is exhausted, the cysteines of cellular proteins become sulfhydryl donors to NAPQI, binding covalently and initiating a cascade of oxidative and cellular damage, resulting in necrosis and, ultimately, liver failure. Thus, avoiding excessive NAPQI formation is an important strategy when using acetaminophen, although to date acetaminophen-sparing has not been an approach any manufacturers have chosen to take. However, due to the prevalence of acetaminophen in many over-the-counter products, it is prudent to consider acetaminophen-sparing precautions when considering combination therapy lasting more than a few days to avoid an inadvertent reduction in glutathione stores.

Thus, various options for pain management are available that are both IR and MR, and contain either a single drug or a combination of analgesics. While these combination products provide the benefits associated with combining two analgesics as described above, both IR and MR, in itself, have a significant disadvantage. IR combination products lack the advantages of MR products described previously. MR combination products lack a significant benefit associated with IR products—rapid onset of analgesia—that is extremely desirable for pain management. Because MR products retard the rate of drug release to sustain the drug effect over prolonged period, release of drug is slow resulting in significant time before effective analgesic drug concentration is attained in the bloodstream. There exists a clinical need for pain management that combines the desirable features of IR and MR in combination pain products.

SUMMARY OF THE INVENTION

Among the various aspects of the present disclosure is a pharmaceutical composition for extended release of oxycodone and acetaminophen comprising at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and at least one extended release component. The composition, when orally administered to a subject, maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition. Additionally, at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration.

A further aspect of the disclosure encompasses a pharmaceutical composition for extended release of oxycodone and acetaminophen comprising (a) at least one immediate release portion comprising oxycodone, acetaminophen or a combination thereof, and (b) at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component, wherein about 30% of the oxycodone in the pharmaceutical composition is released in about 15 minutes and at least about 90% of the acetaminophen in the pharmaceutical composition is released in about 8 hours when measured in 900 ml of 0.1N HCl using a USP type II apparatus at a paddle speed of about 100 rpm and a constant temperature of 37° C.

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Yet another aspect of the disclosure provides a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component, wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 100 rpm in 900 ml of 0.1N HCl using a USP type II apparatus at a constant temperature of 37° C., about 30%, by weight, of the oxycodone or salt thereof is released at about 15 minutes in the test and at least about 90%, by weight, of the acetaminophen is released at about 8 hours in the test. Further, upon oral administration of a single dose of the composition to a subject in need of analgesia, the composition provides a C_{max} for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg, a C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg, a T_{max} for oxycodone from about 2 hours to about 7 hours, and a T_{max} for acetaminophen from about 0.5 hour to about 6 hours.

In a further aspect of the disclosure provides a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component; wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg. Moreover, upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 150 rpm in 900 ml of 0.1N HCl using a USP type II apparatus at a constant temperature of 37° C., no more than about 65%, by weight, of the total amount of the oxycodone or salt is released and no more than about 75%, by weight, of the total amount of the acetaminophen is released after 2 hours; from about 65% to about 85%, by weight, of the total amount of the oxycodone or salt is released and from about 70% to about 90%, by weight, of the total amount of the acetaminophen is released after 4 hours; from about 85% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 85% to about 100%, by weight, of the total amount of the acetaminophen is released after 8 hours; and from about 95% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 90% to about 100%, by weight, of the total amount of the acetaminophen is released after 12 hours.

An additional aspect of the disclosure provides for a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component; wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg. And upon oral administration of the composition in an amount of about 15 mg oxycodone or salt and about 650 mg acetaminophen, the composition provides an $AUC_{0-1.7h}$ for acetaminophen of about 5.0 ng·h/mL/mg to about 13.0 ng·h/mL/mg; an $AUC_{1.7-48h}$ for acetaminophen of about 25.0 ng·h/

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mL/mg to about 75.0 ng·h/mL/mg; an $AUC_{0-2.8h}$ for oxycodone or salt of about 1.0 ng·h/mL/mg to about 3.0 ng·h/mL/mg; and $AUC_{2.8-48h}$ of about 7.5 ng·h/mL/mg to about 15.0 ng·h/mL/mg.

Still another aspect of the disclosure provides a dosage form comprising (a) an immediate release portion comprising acetaminophen and oxycodone, wherein the immediate release portion comprises, by weight of the immediate release portion, from about 70% to about 80% of acetaminophen and from about 0.5% to about 1% of oxycodone; and (b) an extended release portion comprising acetaminophen, oxycodone, and an extended release polymer, wherein the extended release portion comprises, by weight of the extended release portion, from about 20% to about 40% of acetaminophen, from about 0.5% to about 2% of oxycodone, and from about 30% to about 50% of the extended release polymer.

Another aspect provides a dosage form comprising from about 7.5 mg to about 30 mg of oxycodone and from about 325 mg to about 650 mg of acetaminophen. The dosage form comprises (a) at least one immediate release portion comprising about 25% of the total amount of oxycodone in the composition and about 50% of the total amount of acetaminophen in the composition; and (b) at least one extended release portion comprising about 75% of the total amount of oxycodone in the composition, about 50% of the total amount of acetaminophen in the composition, and about 35% to about 45%, by weight of the at least one extended release portion, of an extended release polymer comprising a polyethylene oxide.

A further aspect of the disclosure provides a method for reducing the risk of acetaminophen-induced hepatic damage in a subject being treated for pain with a dosage regimen that comprises administering to the subject at least two consecutive doses of a pharmaceutical composition comprising oxycodone and acetaminophen. The method comprises (a) administering a first dose of the pharmaceutical composition comprising at least one extended release portion comprising acetaminophen, oxycodone or a combination thereof, and an extended release component to the subject, wherein the composition maintains a therapeutic blood plasma concentration of oxycodone of at least 5 ng/mL from about 0.75 hours to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration; and (b) administering a second dose of the pharmaceutical composition to the subject at about 12 hours after administration of the first dose.

Yet another aspect of the disclosure encompasses a method for treating pain in a subject in need thereof with a pharmaceutical composition that comprises oxycodone and acetaminophen. The method comprises orally administering to the subject an effective amount of the pharmaceutical composition comprising at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component, wherein the composition maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma con-

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centration that is less than about 30% of acetaminophen's maximum plasma concentration.

Other features and aspects of the disclosure are described in detail below.

REFERENCE TO COLOR FIGURES

This application file contains at least one drawing executed in color. Copies of this patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 presents the in vitro release profile of oxycodone from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35 wt % POLYOX® 1105, 45 wt % POLYOX® 1105, or 45 wt % POLYOX® N60K, as indicated.

FIG. 2 shows the in vitro release profile of acetaminophen from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35 wt % POLYOX® 1105, 45 wt % POLYOX® 1105, or 45 wt % POLYOX® N60K, as indicated.

FIG. 3 presents the in vitro release profile of oxycodone from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

FIG. 4 presents the in vitro release profile of acetaminophen from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

FIG. 5 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval.

FIG. 6 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 7 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

FIG. 8 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

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FIG. 9 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

FIG. 10 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

FIG. 11 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

FIG. 12 shows the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

FIG. 13 presents the mean plasma concentrations of oxycodone versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 14 shows the mean plasma concentrations of oxycodone versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 15 presents the mean plasma concentrations of acetaminophen versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 16 shows mean plasma concentrations of acetaminophen versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

FIG. 17 illustrates the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 150 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 2 hours.

FIG. 18 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 150

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rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 2 hour period.

FIG. 19 shows the mean plasma concentrations of oxycodone as a function of time by treatment following oral administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 20 presents the mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

FIG. 21 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 22 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

FIG. 23 shows a deconvolution plot of the biphasic absorption of oxycodone from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of oxycodone is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; squares represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and the immediate release 7.5 oxycodone/325 acetaminophen tablet is shown in a solid line with no symbols.

FIG. 24 presents a deconvolution plot of the biphasic absorption of acetaminophen from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of acetaminophen is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; triangles represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and squares represent the immediate release 7.5 oxycodone/325 acetaminophen product.

FIG. 25 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

FIG. 26 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen

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administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

FIG. 27A is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation. FIG. 27B is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled. FIG. 27C is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

FIG. 28A is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation. FIG. 28B is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled. FIG. 28C is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

FIG. 29A presents the mean plasma concentrations and Partial AUCs of acetaminophen (e.g., $AUC_{0-1.7h}$ and $AUC_{1.7-48h}$) versus time by treatment: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

FIG. 29B presents the mean plasma concentrations and Partial AUCs of oxycodone (e.g., $AUC_{0-2.8h}$ and $AUC_{2.8-48h}$) versus time by treatment: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

FIG. 30A presents the mean plasma concentrations and Partial AUCs of oxycodone versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

FIG. 30B presents the mean plasma concentrations and Partial AUCs of acetaminophen versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

FIG. 31 presents oxycodone dissolution data from crushed and intact immediate release tablets containing 7.5 mg oxycodone and 325 mg acetaminophen.

FIGS. 32A and 32B present acetaminophen dissolution data from crushed and intact pharmaceutical formulations described herein containing a total of 7.5 mg oxycodone and a total of 325 mg acetaminophen per tablet.

FIGS. 33A and 33B present oxycodone HCl dissolution data from crushed and intact pharmaceutical formulations described herein containing a total of 7.5 mg oxycodone and a total of 325 mg acetaminophen per tablet.

FIG. 34 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. The dissolu-

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tion data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The three pharmaceutical formulations contained 25% by weight POLYOX® 205, 1105, and N-60K, respectively.

FIG. 35 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 34.

FIG. 36 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The three pharmaceutical formulations contained 45% by weight POLYOX® 205, 1105, and N-60K, respectively.

FIG. 37 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 36.

FIG. 38 presents acetaminophen dissolution data for four pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The four pharmaceutical compositions contained 25% by weight, 35% by weight, 45% by weight, and 55% by weight POLYOX® 1105, respectively.

FIG. 39 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 38.

FIG. 40 presents the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 8 hours.

FIG. 41 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 8 hour period.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein is a combination product of oxycodone and acetaminophen that has the desirable attributes of both IR and MR products. The extended release pharmaceutical composition disclosed herein comprises at least one extended release portion and, optionally, at least one immediate release portion. The extended release and immediate release portions may comprise oxycodone, acetaminophen, or combinations thereof. The at least one immediate release portion releases acetaminophen (APAP) and/or oxycodone instantly in an immediate release fashion that provides rapid onset for the attainment of therapeutically effective plasma concentrations within about the first 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition. The at least one extended release portion releases acetaminophen and/or oxycodone in an extended release fashion to maintain plasma concentrations above the minimum effective concentration for about 8-12 hours. In addition, two other important features of this composition are: 1) to allow the plasma concentrations of oxycodone to fall as rapidly as an immediate release formulation to provide the same rate of termination of drug effects as the immediate release product, and 2) to allow the concentrations of APAP to fall even quicker towards the later part of the dosing interval and bring down the levels of APAP lower than those of the immediate release product. The concentrations of

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APAP in the last quarter of the dosing interval are comparable to the pre-dose concentrations in a multiple dose setting, allowing for the glutathione synthase enzyme cycle to replenish the body's levels of glutathione to avoid the formation of toxic intermediates with subsequent doses of APAP. Moreover, the concentrations of APAP in the later part of the dosing interval are lower than those present when administered a conventional extended release formulation. This feature has been deliberately introduced to reduce the hepatic injury due to APAP and is termed "APAP time-off".

Abuse potential is a concern with any opioid product. The addition of APAP to the opioid, however, is likely to reduce the amount of abuse by illicit routes of administration, particularly intravenous or intranasal administration. This deterrence is likely due to the bulk (grams) that the APAP provides as well as the relative aqueous insolubility compared to freely soluble opioid salts. Further, APAP is known to be irritating to nasal passages and to make drug abusers sneeze violently when they are trying to snort it. In addition, embodiments disclosed herein may be tamper resistant in that the compositions are difficult to crush for administration intravenously or intranasally; difficult to extract with water or alcohol because the mixture becomes too viscous for injecting or snorting; and resistant to dose dumping in alcohol.

In one embodiment, the pharmaceutical composition disclosed herein, therefore, provides: 1) rapid onset of analgesia within about 15, 30, 45, or 60 minutes after administration of the composition mediated by both oxycodone and APAP, with APAP providing maximal contribution during the early phase; 2) prolonged analgesia for the entire 12 hours period, mainly contributed by oxycodone, with minimal fluctuations during this period; 3) relatively low levels of APAP toward end of dosing interval to allow for recovery of the depleted hepatic glutathione system; 4) low abuse quotient; and 5) abuse deterrence.

Headings included herein are simply for ease of reference, and are not intended to limit the disclosure in any way.

I. Definitions

Compounds useful in the compositions and methods include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, as well as racemic mixtures and pure isomers of the compounds described herein, where applicable.

When introducing elements of the various embodiment(s) of the present disclosure, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

The use of individual numerical values are stated as approximations as though the values were preceded by the word "about" or "approximately." Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about" or "approximately." In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms "about" and "approximately" when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered

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include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words “about” or “approximately” will serve to broaden a particular numerical value or range. Thus, as a general matter, “about” or “approximately” broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term “about” or “approximately.” Consequently, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

The term “abuse quotient” for a pharmaceutical composition as used herein is the numerical value obtained via dividing the C_{max} for a drug by the T_{max} for the same drug. Generally speaking, the abuse quotient provides a means for predicting the degree of addictiveness of a given pharmaceutical composition. Pharmaceutical compositions with lower abuse quotients typically are less addictive compared to pharmaceutical compositions with higher abuse quotients.

The term “active agent” or “drug,” as used herein, refers to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor from eliciting a physiological response.

The term “bioequivalent,” as used herein, refers to two compositions, products or methods where the 90% Confidence Intervals (CI) for AUC, partial AUC and/or C_{max} are between 0.80 to 1.25.

The term “bulk density,” as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

The term “content uniformity,” as used herein refers to the testing of compressed tablets to provide an assessment of how uniformly the micronized or submicron active ingredient is dispersed in the powder mixture. Content uniformity is measured by use of USP Method (General Chapters, Uniformity of Dosage Forms), unless otherwise indicated. A plurality refers to five, ten or more tablet compositions.

The term “friability,” as used herein, refers to the ease with which a tablet will break or fracture. The test for friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of composition abraded or chipped is calculated.

The term “ER” as used herein refers to extended release. The phrases “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” are used interchangeably in this document. Further, as used herein the “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” can be either (i) a discrete part(s) of the

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pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

The term “IR” as used herein refers to immediate release. The phrases “immediate release layer,” “IR layer,” “IR portion” and “immediate release portion” are used interchangeably in this document. In addition, as used herein the “immediate release layer,” “IR layer,” “IR portion” and “immediate release portion” can be either (i) a discrete part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

The term “half life” as used herein refers to the time required for a drug’s blood or plasma concentration to decrease by one half. This decrease in drug concentration is a reflection of its excretion or elimination after absorption is complete and distribution has reached an equilibrium or quasi equilibrium state. The half life of a drug in the blood may be determined graphically off of a pharmacokinetic plot of a drug’s blood-concentration time plot, typically after intravenous administration to a sample population. The half life can also be determined using mathematical calculations that are well known in the art. Further, as used herein the term “half life” also includes the “apparent half-life” of a drug. The apparent half life may be a composite number that accounts for contributions from other processes besides elimination, such as absorption, reuptake, or enterohepatic recycling.

“Optional” or “optionally” means that the subsequently described element, component or circumstance may or may not occur, so that the description includes instances where the element, component, or circumstance occurs and instances where it does not.

“Partial AUC” means an area under the drug concentration-time curve (AUC) calculated using linear trapezoidal summation for a specified interval of time, for example, $AUC_{(0-1hr)}$, $AUC_{(0-2hr)}$, $AUC_{(0-4hr)}$, $AUC_{(0-6hr)}$, $AUC_{(0-8hr)}$, $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$, $AUC_{(0-(x)hr)}$, $AUC_{(x-y)hr}$, $AUC_{(T_{max}-t)}$, $AUC_{(0-t)hr}$, $AUC_{(T_{max} \text{ of IR product}+2SD-t)}$, or $AUC_{(0-\infty)}$.

A drug “release rate,” as used herein, refers to the quantity of drug released from a dosage form or pharmaceutical composition per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically measured as an in vitro rate of dissolution, i.e., a quantity of drug released from the dosage form or pharmaceutical composition per unit time measured under appropriate conditions and in a suitable fluid. The specific results of dissolution tests claimed herein are performed on dosage forms or pharmaceutical compositions immersed in 900 mL of 0.1N HCl using a USP Type II apparatus at a paddle speed of either about 100 rpm or about 150 rpm and a constant temperature of about 37° C. Suitable aliquots of the release rate solutions are tested to determine the amount of drug released from the dosage form or pharmaceutical composition. For example, the drug can be assayed or injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

The terms “subject” or “patient” are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, humans. The term “tap density” or “tapped density,” as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

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II. Pharmaceutical Compositions Comprising Extended and Immediate Release Portions Comprising Oxycodone and Acetaminophen

The present disclosure provides pharmaceutical compositions comprising oxycodone and its pharmaceutical salts and acetaminophen. The pharmaceutical composition comprises at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component. The pharmaceutical composition may also comprise at least one immediate release portion comprising oxycodone, acetaminophen, or a combination thereof. The compositions disclosed herein are formulated to deliver therapeutic concentrations of oxycodone and acetaminophen within about the first hour after oral administration and to maintain therapeutic concentrations of oxycodone and acetaminophen for an extended period of time (e.g., 10-12 hours).

The total amount of oxycodone present in the pharmaceutical composition can and will vary. In some embodiments, the total amount of oxycodone present in the pharmaceutical composition may range from about 2 mg to about 160 mg, about 5 mg to about 75 mg, about 5 mg to about 40 mg, or about 10 mg to about 30 mg. In another embodiment, the total amount of oxycodone in the pharmaceutical composition may range from about 5 mg to about 30 mg. In various embodiments, the total amount of oxycodone present in the pharmaceutical composition may be about 5 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, or 160 mg. In one embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 30 mg. In another embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 15 mg. In still another embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 7.5 mg.

The total amount of acetaminophen present in the pharmaceutical composition also may vary. In one embodiment, the total amount of acetaminophen present in the pharmaceutical composition may range from about 80 mg to about 1600 mg. In another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 250 mg to about 1300 mg. In a further embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 300 mg to about 600 mg. In yet another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 325 mg to about 650 mg. In another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 1000 mg, or 1300 mg. In one embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 650 mg. In another embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 500 mg. In yet another embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 325 mg.

(a) Immediate Release Portion

The pharmaceutical composition disclosed herein may comprise at least one immediate release portion. In one embodiment, the at least one immediate release portion may

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comprise oxycodone. In another embodiment, the at least one immediate release portion may comprise acetaminophen. In a further embodiment, the at least one immediate release portion may comprise oxycodone and acetaminophen.

The at least one immediate release portion of the pharmaceutical composition is designed to release more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) within about one hour. In one embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 45 min. In another embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 30 min. In a further embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 20 min. In yet another embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 15 min. In an alternate embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion(s) may be released in less than about 10 min. In yet another embodiment, more than 80%, more than 90%, or essentially all of the oxycodone and/or acetaminophen in the at least one immediate release portion may be released in less than about 5 min.

(i) Oxycodone

The at least one immediate release portion of the pharmaceutical composition may comprise oxycodone. The amount of oxycodone in the at least one immediate release portion of the pharmaceutical composition can and will vary. In one embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1 mg to about 40 mg. In a further embodiment, the amount of oxycodone in the at least one immediate release portion of the pharmaceutical composition may range from about 1 mg to about 7.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 7.5 mg to about 15 mg. In yet another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 15 mg to about 40 mg. In various embodiments, the amount of oxycodone in the at least one immediate release portion may be about 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 11.0 mg, 12.0 mg, 13.0 mg, 14.0 mg, 15.0 mg, 20.0 mg, or 40.0 mg. In one embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 7.0 mg and about 8.0 mg, for example, about 7.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may be between about 3.0 mg and about 4.0 mg, for example, about 3.75 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may be between about 1.0 mg and about 2.0 mg, for example, about 1.875 mg.

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The amount of oxycodone present in the at least one immediate release portion(s) may be expressed as a percentage (w/w) of the total amount of oxycodone in the pharmaceutical composition. In one embodiment, the at least one immediate release portion may comprise from about 20% to about 30% (w/w) of the total amount of oxycodone present in the pharmaceutical composition. In certain embodiments, the percentage of oxycodone present in the at least one immediate release portion of the pharmaceutical composition may be about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% (w/w) of the total amount of oxycodone. In another embodiment, the percentage of oxycodone present in the at least one immediate release portion of the pharmaceutical composition may be about 25% (w/w) of the total amount of oxycodone present in the pharmaceutical composition.

The amount of oxycodone in the at least one immediate release portion also may be expressed as a percentage (w/w) of the total weight of the immediate release portion(s) of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an immediate release portion may range from about 0.2 (w/w) to about 15.0% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In another embodiment, the amount of oxycodone in an immediate release portion may range from about 0.5% (w/w) to about 2% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion may comprise an amount of oxycodone that is approximately 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.25%, 7.5%, 7.75%, 8.0%, 8.25%, 8.5%, 8.75%, 9.0%, 9.25%, 9.5%, 9.75%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In yet another embodiment, the amount of oxycodone in an immediate release portion may be about 0.5% (w/w) to about 1.0% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

In some embodiments, the oxycodone of the at least one immediate release portion(s) of the pharmaceutical composition may be in the form of particles comprising oxycodone and at least one excipient. The at least one immediate release portion, therefore, may comprise particles of oxycodone that are admixed with the acetaminophen and optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety. The oxycodone particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Acetaminophen

The at least one immediate release portion of the pharmaceutical composition may comprise acetaminophen. The

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amount of acetaminophen in the at least one immediate release portion(s) can and will vary. In one embodiment, the amount of acetaminophen in the at least one immediate release portion of the pharmaceutical composition may range from about 40 mg to about 800 mg. In still another embodiment, the at least one immediate release portion of the pharmaceutical composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one immediate release portion may comprise from about 125 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 500 mg, 520 mg, 650 mg, or 780 mg. In one embodiment, the at least one immediate release portion may comprise about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 125 mg.

The at least one immediate release portion(s) of the pharmaceutical composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. The amount of acetaminophen in the at least one immediate release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. In one embodiment, the percentage of acetaminophen present in the at least one immediate release portion may be about 50% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition.

The amount of acetaminophen in an immediate release portion(s) of the pharmaceutical composition may range from about 20% (w/w) to about 95% (w/w) of the total weight of such immediate release portion of the composition. In various embodiments, an immediate release portion may comprise an amount of acetaminophen that is approximately about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, or 95% (w/w) of the total weight of such immediate release portion. In one embodiment, the amount of acetaminophen in an immediate release portion may range from about 70% to about 80% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

(iii) Excipients

The at least one immediate release portion(s) of the pharmaceutical composition may further comprise at least one excipient. Suitable excipients include binders, fillers, disintegrants, lubricants, antioxidants, chelating agents, and color agents.

In one embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one binder. Suitable binders include, without limit,

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starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxylcellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an immediate release portion of the pharmaceutical composition may range from about 5% to about 10% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the pharmaceutical composition may comprise at least one binder that is present in an amount that is about 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, or 9.0% (w/w) of such immediate release portion of the composition.

In another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an immediate release portion may range from about 1.0% to about 10.0% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the pharmaceutical composition may comprise at least one filler that is present in an amount that is about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.2%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, or 10.0%, of such immediate release portion of the pharmaceutical composition.

In still another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may further comprise a disintegrant. The disintegrant may be selected from the group consisting of croscarmellose sodium, crospovidone, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, low substituted hydroxypropylcellulose, microcrystalline cellulose, and sodium starch glycolate. In one embodiment, the amount of disintegrant in an immediate release portion may range from about 2.0% to about 15.0% (w/w) of the total weight of such immediate release portion. In some embodiments, the amount of disintegrant in an immediate release portion may be about 4.0%, 4.2%, 4.4%, 4.6%, 4.8%, 5.0%, 5.2%, 5.4%, 5.6%, 5.8%, 6.0%, 6.2%, 6.4%, 6.6%, 6.8%, or 7.0% (w/w) of such immediate release portion of the pharmaceutical composition.

In a further embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may further comprise a lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may

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be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of an immediate release portion. In certain embodiments, the amount of lubricant in at least one immediate release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.55%, 1.6%, 1.65%, 1.7%, 1.75%, 1.80%, 1.85%, 1.90%, or 2.0% (w/w) of the total weight of such immediate release portion.

In yet another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one antioxidant. Suitable antioxidants include, without limitation, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphatocopherol, and propylgallate. The amount of antioxidant present in an immediate release portion of the pharmaceutical composition may range from about 0.01% to about 4.0% (w/w), or from about 0.02% to about 0.10% (w/w) of the total weight of such immediate release portion. In various embodiments, the amount of antioxidant present in an immediate release portion of the pharmaceutical composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such immediate release portion.

In still another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo) tetracetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N'',N'''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicycysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N'',N'''-tetraacetic acid. In one embodiment, the chelating agent may be the sodium salt of EDTA. The amount of chelating agent present in an immediate release portion of the pharmaceutical composition may range from about 0.001% to about 0.20% (w/w) of such immediate release portion. In some embodiments, the amount of chelating agent present in an immediate release portion of the pharmaceutical composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such immediate release portion.

In an alternate embodiment, the at least one immediate release portion of the pharmaceutical composition may comprise a color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an immediate release portion may range from about 2.0% to about 5.0% (w/w) of the total weight of such immediate release portion of the composition. In other embodiments, the amount of color agent present in an immediate release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of the total weight of such immediate release portion.

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(b) Extended Release Portion

The pharmaceutical composition disclosed herein comprises at least one extended release portion. The at least one extended release portion may comprise oxycodone, acetaminophen, or a combination thereof. The extended release portion(s) further comprise(s) an extended release component. The extended release component may comprise at least one extended release polymer.

The at least one extended release portion of the pharmaceutical composition is designed to release the active agents over an extended period of time. In general, the extended release portion(s) provides release of oxycodone and/or acetaminophen for a period of time ranging from at least about 3 hours (hrs) to at least about 12 hrs. In one embodiment, the extended release portion(s) may release oxycodone and/or acetaminophen over a period of at least about 5 hrs, or over a period at least about 6 hrs. In another embodiment, oxycodone and/or acetaminophen may be released from the extended release portion(s) over a period of at least about 7 hrs, or over a period of at least about 8 hrs. In still another embodiment, the extended release portion(s) may release oxycodone and/or acetaminophen over a period of at least about 9 hrs, or over a period of at least about 10 hrs. In a further embodiment, oxycodone and/or acetaminophen may be released from the extended release portion(s) over a period of at least about 11 hrs, or over a period of at least about 12 hrs.

(i) Oxycodone

The amount of oxycodone present in the at least one extended release portion(s) can and will vary. In one embodiment, the amount of oxycodone in the at least one extended release portion may range from about 1 mg to about 120 mg. In a further embodiment, the at least one extended release portion of the pharmaceutical composition may comprise about 1 mg to about 22.5 mg of oxycodone. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 10 mg to about 30 mg. In yet another embodiment, the amount of oxycodone in the at least one extended release portion may be about 30 mg to about 60 mg. In another embodiment, the at least one extended release portion comprises about 5 mg to about 7 mg of oxycodone. In a further embodiment, the amount of oxycodone may be about 5.625 mg to about 11.25 mg. In an additional embodiment, the amount of oxycodone may be about 10 mg to about 12.5 mg. In a further embodiment, the amount of oxycodone may be about 12 mg to about 18 mg. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 20 mg to about 25 mg. In yet another embodiment, the amount of oxycodone may be about 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 5.625 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10.0 mg, 10.5 mg, 11.0 mg, 11.25 mg, 11.5 mg, 12.0 mg, 12.5 mg, 13.0 mg, 13.5 mg, 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 22.5 mg, or 25 mg. In one embodiment, the amount of oxycodone in the at least one extended release portion may be from about 22 mg to about 23 mg, for example, about 22.5 mg. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 10 mg to about 12 mg, for example, about 11.25 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may be from about 5 mg to about 6 mg, for example, about 5.625 mg.

The amount of oxycodone present in the at least one extended release portion(s) may be expressed as a percentage of the total amount of oxycodone in the pharmaceutical composition. In one embodiment, the at least one extended release

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portion of the pharmaceutical composition comprises from about 70% to about 80% (w/w) of the total amount of oxycodone present in the pharmaceutical composition. In certain embodiments, the percentage of oxycodone present in the at least one extended release portion of the pharmaceutical composition may be about 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% of the total amount of oxycodone. In one embodiment, the percentage of oxycodone present in the at least one extended release portion of the pharmaceutical composition may be about 75% of the total amount of oxycodone present in the pharmaceutical composition.

The amount of oxycodone in the extended release portion(s) also may be expressed as a percentage of the total weight of the extended release portion(s) of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an extended release portion may range from about 0.5% to about 5.0% (w/w) of the total weight of the such extended release portion of the pharmaceutical composition. In various embodiments, an extended release portion may comprise an amount of oxycodone that is approximately 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, or 4.0% (w/w) of the total weight of such extended release portion of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an extended release portion comprises about 0.5% to about 2% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

In some embodiments, the oxycodone of the extended release portion(s) may be in the form of particles comprising oxycodone and at least one excipient. Thus, the at least one extended release portion may comprise particles of oxycodone which are admixed with the acetaminophen and the extended release component, both of which are detailed below, as well as optional excipients. Suitable oxycodone particles are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety. The oxycodone particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d₅₀) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d₉₀) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Acetaminophen

The extended release portion(s) of the pharmaceutical composition may comprise acetaminophen. The amount of acetaminophen in the extended release portion(s) of the pharmaceutical composition can and will vary. In one embodiment, the at least one extended release portion of the pharmaceutical composition may comprise an amount of acetaminophen ranging from about 40 mg to about 800 mg. In still another embodiment, the at least one extended release portion of the pharmaceutical composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one extended release portion may comprise from about 125 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of

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acetaminophen in the at least one extended release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 500 mg, 520 mg, 650 mg, or 780 mg. In one embodiment, the at least one extended release portion comprises about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 125 mg.

The extended release portion(s) of the pharmaceutical composition may comprise from about 40% to about 60% of the total amount of acetaminophen present in the pharmaceutical composition. The amount of acetaminophen in the at least one extended release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. In one embodiment, the percentage of acetaminophen present in the extended release portion(s) of the pharmaceutical composition may be about 50% (w/w) of the total amount of acetaminophen.

The amount of acetaminophen in an extended release portion of the pharmaceutical composition may range from about 15% to about 60% (w/w) of the total weight of such extended release portion of the pharmaceutical composition. In various embodiments, an extended release portion may comprise an amount of acetaminophen that is approximately about 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 30%, 32%, 35%, 37%, 40%, 42%, 45%, 47%, 50%, 52%, or 55% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of acetaminophen in an extended release portion may range from about 20% to about 40% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

(iii) Extended Release Component

The extended release portion(s) of the pharmaceutical composition also comprise(s) an extended release component. Suitable extended release components include polymers, resins, hydrocolloids, hydrogels, and the like.

In one embodiment, the extended release component may comprise at least one extended release polymer. Suitable polymers for inclusion in the at least one extended release portion of the pharmaceutical composition may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, such as random copolymers, block copolymers, and graft copolymers. Suitable hydrophilic polymers include, but are not limited to: polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers; cellulosic polymers, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, microcrystalline cellulose, and polysaccharides and their derivatives; acrylic acid and meth-

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acrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate; maleic anhydride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); polyalkylene oxides; poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; xanthan gum; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate. The polymers may be used individually or in combination. Certain combinations will often provide a more controlled release of oxycodone and acetaminophen than their components when used individually. Suitable combinations include cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum, and poly(ethylene oxide) combined with xanthan gum.

In one embodiment, the extended release polymer(s) may be a cellulosic polymer, such as an alkyl substituted cellulose derivative as detailed above. In terms of their viscosities, one class of exemplary alkyl substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C.

In one embodiment, the extended release polymer(s) may be a polyalkylene oxide. In another aspect, the polyalkylene oxide may be poly(ethylene oxide). In a further embodiment, the poly(ethylene oxide) may have an approximate molecular weight between 500,000 Daltons (Da) to about 10,000,000 Da or about 900,000 Da to about 7,000,000 Da. In yet a further embodiment, the poly(ethylene oxide) may have a molecular weight of approximately 600,000 Da, 700,000 Da, 800,000 Da, 900,000 Da, 1,000,000 Da, 2,000,000 Da, 3,000,000 Da, 4,000,000 Da, 5,000,000 Da, 6,000,000 Da, 7,000,000 Da, 8,000,000 Da, 9,000,000 Da, or 10,000,000 Da.

In another embodiment, the polyethylene oxide may be any desirable grade of POLYOX™ or any combination thereof. By way of example and without limitation, the POLYOX™ grade may be WSR N-10, WSR N-80, WSR N-750, WSR 205, WSR 1105, WSR N-12K, WSR N-60K, WSR-301, WSR Coagulant, WSR-303, WSR-308, WSR N-3000, UCARFLOC Polymer 300, UCARFLOC Polymer 302, UCARFLOC Polymer 304, and UCARFLOC Polymer 309. In one embodiment, the polyethylene oxide may have an average molecular weight of from about 100,000 Da to about 8,000,000 Da. In another embodiment, the polyethylene oxide may have an average molecular weight of about 100,000 Da, about 200,000 Da, about 300,000 Da, about 400,000 Da, about 600,000 Da, about 900,000 Da, about 1,000,000

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Da, about 2,000,000 Da, about 4,000,000 Da, about 5,000,000 Da, about 7,000,000 Da, or about 8,000,000 Da. In still another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units ($-\text{CH}_2\text{CH}_2\text{O}-$) of about 2,000 to about 160,000. In yet another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units of about 2,275, about 4,500, about 6,800, about 9,100, about 14,000, about 20,000, about 23,000, about 45,000, about 90,000, about 114,000, or about 159,000.

The release profile of the extended release pharmaceutical composition disclosed herein will depend partially upon the molecular weight of the extended release polymer(s). In certain embodiments, the polymers are of a moderate to high molecular weight (900,000 Da to 4,000,000 Da) to control release of oxycodone and/or acetaminophen from the composition via diffusion of the active agent(s) out of the polymer and/or erosion of the polymer. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of about 900,000 Da to about 2,000,000 Da. Using a lower molecular weight ("MW") polyethylene oxide, such as POLYOX® 1105 (900,000 MW), the release rates for both drugs are higher. Using a higher molecular weight polyethylene oxide (such as POLYOX® N-60K (2,000,000 MW) or POLYOX® WSR-301 (4,000,000 MW) reduces the rate of release for both drugs. In another embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight is utilized so that the viscosity of a 2% aqueous solution is about 4000 cps to greater than about 100,000 cps.

The release profile of the extended release pharmaceutical composition disclosed herein may also depend upon the amount of the extended release polymer(s) in the pharmaceutical composition. In general, the release rates for oxycodone and/or acetaminophen may be decreased by increasing the amount of the extended release polymer(s) in the pharmaceutical composition. By way of example and without limitation, the release profile of acetaminophen and oxycodone may be decreased by increasing the amount of POLYOX® 1105 from about 25% by weight of the ER portion to about 35% by weight of the ER portion.

The amount of extended release polymer or polymers present in the extended release portion(s) of the pharmaceutical composition can and will vary. In one embodiment, the polymer present in an extended release portion of the pharmaceutical composition may range from about 15% to about 70% (w/w), or about 20% to about 60% (w/w), or about 25% to about 55% (w/w) of the total weight of such extended release portion of the dosage form. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 30% to about 50% (w/w) of the total weight of such extended release portion. In still another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 35% to about 45% (w/w) of the total weight of such extended release portion. In yet another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 30%, 35%, 40%, 45%, 50%, 55%, or 60% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 35% (w/w) of the total weight of such extended release portion. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 45% (w/w) of the total weight of such extended release portion. In one embodi-

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ment, the ER layer swells upon imbibition of fluid to a size which is about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% larger than the size of the ER layer prior to imbibition of fluid.

In another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 25% larger than the size of the ER layer prior to imbibition of fluid within about 15 minutes of the start of fluid imbibition. In still another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 100% larger than the size of the ER layer prior to imbibition of fluid within about 45 min, 50 min, 60 min, 75 min, or 90 min of the start of fluid imbibitions.

(iv) Excipients

The extended release portion(s) of the pharmaceutical composition may further comprise at least one excipient. Suitable excipients include binders, fillers, lubricants, antioxidants, chelating agents, and color agents.

In one embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxylcellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an extended release portion of the pharmaceutical composition may range from about 0.5% to about 8.0% (w/w) of such extended release portion. In various embodiments, an extended release portion of the pharmaceutical composition may comprise at least one binder that is present in an amount that is about 0.5%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, or 8.0% (w/w) of such extended release portion of the dosage form.

In another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an extended release portion may range from about 2% to about 50% (w/w) of the total weight of such extended release portion. In various embodiments, an extended release portion of the pharmaceutical composition may comprise at least one filler that is present in an amount that is about 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, or 45% (w/w) of such extended release portion of the dosage form.

In a further embodiment, the extended release portion(s) of the pharmaceutical composition may further comprise a lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycer-

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ides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of such extended release portion. In certain embodiments, the amount of lubricant in an extended release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.75%, 1.80%, 1.85%, 1.90%, or 2.0% (w/w) of the total weight of such extended release portion.

In yet another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one antioxidant. Suitable antioxidants include, without limit, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, and propylgallate. The amount of antioxidant present in an extended release portion of the pharmaceutical composition may range from about 0.01% to about 4.0%, or from about 0.02% to about 0.10% (w/w). In various embodiments, the amount of antioxidant present in an extended release portion of the pharmaceutical composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such extended release portion.

In still another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetraacetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N'',N'''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicycysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N'',N'-tetraacetic acid. In one embodiment, the chelating agent is the sodium salt of EDTA. The amount of chelating agent present in an extended release portion of the pharmaceutical composition may range from about 0.001% to about 0.20% (w/w) of such extended release portion. In some embodiments, the amount of chelating agent present in an extended release portion of the pharmaceutical composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such extended release portion.

In an alternate embodiment, the extended release portion(s) of the pharmaceutical composition may comprise a color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an extended release portion may range from about 2.0% to about 5.0% (w/w) of such extended release portion of the dosage form. In other embodiments, the amount of color agent present in an extended release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of such extended release portion.

(c) Dosage Forms of the Pharmaceutical Composition

The physical form of the pharmaceutical composition disclosed herein can and will vary. In general, the pharmaceuti-

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cal composition is a solid dosage form comprising at least one extended release portion and, optionally, at least one immediate release portion. Suitable solid dosage forms include tablets, caplets, capsules, encapsulated beads, and gencaps. Non-limiting types of tablets include coated tablets, uncoated tablets, bilayer tablets, multiparticle tablets, monolithic tablets, matrix tablets, compressed tablets, and molded tablets. Non-limiting types of capsules include hard capsules and multi-layer capsules.

In one embodiment, the dosage form may be a capsule. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, hard cellulose capsules, and hydrogel capsules. In one example, the core of the capsule may comprise the at least one extended release portion and the shell of the capsule may comprise the at least one immediate release portion of the composition. In another example, the core of the capsule may comprises one extended release portion, comprising oxycodone, acetaminophen and an extended release component, and the shell of the capsule may comprise one immediate release portion of the composition comprising oxycodone and acetaminophen. In yet another example, the core of the capsule may comprise two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and the shell of the capsule may comprise two immediate release portions of the composition, each comprising one of the oxycodone and the acetaminophen. In still another embodiment, the dosage form may be a sustained release capsule comprising the oxycodone or the acetaminophen and exhibiting immediate release and/or extended release properties.

In another embodiment, the dosage form may be a tablet comprising at least one extended release portion and at least one immediate release portion. The at least one immediate release portion may be adjacent to, abutting, or surrounding the at least one extended release portion. In one embodiment, the dosage form may be a bilayer tablet comprising one extended release layer comprising the oxycodone and the acetaminophen and one immediate release layer comprising the oxycodone and the acetaminophen. The bilayer tablet may comprise a coating. In another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the oxycodone and the acetaminophen, and one immediate release portion comprising both the oxycodone and the acetaminophen. In yet another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the oxycodone and the acetaminophen, and two immediate release portions, each comprising one of the oxycodone and the acetaminophen. In still another embodiment, the dosage form may be a sustained release tablet comprising the oxycodone and/or acetaminophen and exhibiting immediate release and/or extended release properties.

In certain embodiments, the tablet may have a friability of no greater than about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.7% or 1.0%. In another embodiment, the tablet may have a friability of greater than 0 but less than about 1.0%, greater than 0 but less than about 0.5%, greater than 0 but less than about 0.3%, or greater than 0 but less than about 0.2%. In still another embodiment, the tablet may have a friability of zero.

In another embodiment, the tablet may have a hardness of at least about 10 Kilopond (also known as kilopons) (kp). In some embodiments, the tablet may have a hardness of about 9 kp to about 25 kp, or about 12 kp to about 20 kp. In further embodiments, the tablet may have a hardness of about 11 kp, 12 kp, 13 kp, 14 kp, 15 kp, 16 kp, 17 kp, 18 kp, 19 kp, or 20 kp.

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In additional embodiments, the tablet may have a content uniformity of from about 85 to about 115 percent by weight or from about 90 to about 110 percent by weight, or from about 95 to about 105 percent by weight. In other embodiments, the content uniformity may have a relative standard deviation (RSD) equal to or less than about 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1.0%, or 0.5%.

In still other embodiments, prior to administration to a patient or immersion in fluid, the pharmaceutical composition may have (i) a length of approximately 18 mm, 18.01 mm, 18.02 mm, 18.03 mm, 18.04 mm, 18.05 mm, 18.06 mm, 18.07 mm, 18.08 mm, 18.09 mm, 18.1 mm, 18.11 mm, 18.12 mm, 18.13 mm, 18.14 mm, 18.15 mm, 18.16 mm, 18.17 mm, 18.18 mm, 18.19 mm, 18.2 mm, 18.21 mm, 18.22 mm, 18.23 mm, 18.24 mm, 18.25 mm, 18.26 mm, 18.27 mm, 18.28 mm, 18.29 mm, 18.3 mm, 18.31 mm, 18.32 mm, 18.33 mm, 18.34 mm, 18.35 mm, 18.36 mm, 18.37 mm, 18.38 mm, 18.39 mm, 18.4 mm, 18.41 mm, 18.42 mm, 18.43 mm, 18.44 mm, 18.45 mm, 18.46 mm, 18.47 mm, 18.48 mm, 18.49 mm, 18.5 mm, 18.51 mm, 18.52 mm, 18.53 mm, 18.54 mm, 18.55 mm, 18.56 mm, 18.57 mm, 18.58 mm, 18.59 mm, 18.6 mm, 18.61 mm, 18.62 mm, 18.63 mm, 18.64 mm, 18.65 mm, 18.66 mm, 18.67 mm, 18.68 mm, 18.69 mm, 18.7 mm, 18.71 mm, 18.72 mm, 18.73 mm, 18.74 mm, 18.75 mm, 18.76 mm, 18.77 mm, 18.78 mm, 18.79 mm, 18.8 mm, 18.81 mm, 18.82 mm, 18.83 mm, 18.84 mm, 18.85 mm, 18.86 mm, 18.87 mm, 18.88 mm, 18.89 mm, 18.9 mm, 18.91 mm, 18.92 mm, 18.93 mm, 18.94 mm, 18.95 mm, 18.96 mm, 18.97 mm, 18.98 mm, 18.99 mm, 19 mm, 19.01 mm, 19.02 mm, 19.03 mm, 19.04 mm, 19.05 mm, 19.06 mm, 19.07 mm, 19.08 mm, 19.09 mm, 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, 19.3 mm, 19.31 mm, 19.32 mm, 19.33 mm, 19.34 mm, 19.35 mm, 19.36 mm, 19.37 mm, 19.38 mm, 19.39 mm, 19.4 mm, 19.41 mm, 19.42 mm, 19.43 mm, 19.44 mm, 19.45 mm, 19.46 mm, 19.47 mm, 19.48 mm, 19.49 mm, 19.5 mm, 19.51 mm, 19.52 mm, 19.53 mm, 19.54 mm, 19.55 mm, 19.56 mm, 19.57 mm, 19.58 mm, 19.59 mm, 19.6 mm, 19.61 mm, 19.62 mm, 19.63 mm, 19.64 mm, 19.65 mm, 19.66 mm, 19.67 mm, 19.68 mm, 19.69 mm, 19.7 mm, 19.71 mm, 19.72 mm, 19.73 mm, 19.74 mm, 19.75 mm, 19.76 mm, 19.77 mm, 19.78 mm, 19.79 mm, 19.8 mm, 19.81 mm, 19.82 mm, 19.83 mm, 19.84 mm, 19.85 mm, 19.86 mm, 19.87 mm, 19.88 mm, 19.89 mm, 19.9 mm, 19.91 mm, 19.92 mm, 19.93 mm, 19.94 mm, 19.95 mm, 19.96 mm, 19.97 mm, 19.98 mm, 19.99 mm, or 20 mm as measured on the major axis, (ii) a width of approximately 11 mm, 11.01 mm, 11.02 mm, 11.03 mm, 11.04 mm, 11.05 mm, 11.06 mm, 11.07 mm, 11.08 mm, 11.09 mm, 11.1 mm, 11.11 mm, 11.12 mm, 11.13 mm, 11.14 mm, 11.15 mm, 11.16 mm, 11.17 mm, 11.18 mm, 11.19 mm, 11.2 mm, 11.21 mm, 11.22 mm, 11.23 mm, 11.24 mm, 11.25 mm, 11.26 mm, 11.27 mm, 11.28 mm, 11.29 mm, 11.3 mm, 11.31 mm, 11.32 mm, 11.33 mm, 11.34 mm, 11.35 mm, 11.36 mm, 11.37 mm, 11.38 mm, 11.39 mm, 11.4 mm, 11.41 mm, 11.42 mm, 11.43 mm, 11.44 mm, 11.45 mm, 11.46 mm, 11.47 mm, 11.48 mm, 11.49 mm, 11.5 mm, 11.51 mm, 11.52 mm, 11.53 mm, 11.54 mm, 11.55 mm, 11.56 mm, 11.57 mm, 11.58 mm, 11.59 mm, 11.6 mm, 11.61 mm, 11.62 mm, 11.63 mm, 11.64 mm, 11.65 mm, 11.66 mm, 11.67 mm, 11.68 mm, 11.69 mm, 11.7 mm, 11.71 mm, 11.72 mm, 11.73 mm, 11.74 mm, 11.75 mm, 11.76 mm, 11.77 mm, 11.78 mm, 11.79 mm, 11.8 mm, 11.81 mm, 11.82 mm, 11.83 mm, 11.84 mm, 11.85 mm, 11.86 mm, 11.87 mm, 11.88 mm, 11.89 mm, 11.9 mm, 11.91 mm, 11.92 mm, 11.93 mm, 11.94 mm, 11.95 mm, 11.96 mm, 11.97 mm, 11.98 mm, 11.99 mm, 12 mm, 12.01 mm, 12.02 mm, 12.03 mm, 12.04 mm, 12.05 mm,

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12.06 mm, 12.07 mm, 12.08 mm, 12.09 mm, 12.1 mm, 12.11 mm, 12.12 mm, 12.13 mm, 12.14 mm, 12.15 mm, 12.16 mm, 12.17 mm, 12.18 mm, 12.19 mm, 12.2 mm, 12.21 mm, 12.22 mm, 12.23 mm, 12.24 mm, 12.25 mm, 12.26 mm, 12.27 mm, 12.28 mm, 12.29 mm, 12.3 mm, 12.31 mm, 12.32 mm, 12.33 mm, 12.34 mm, 12.35 mm, 12.36 mm, 12.37 mm, 12.38 mm, 12.39 mm, 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, 12.5 mm, 12.51 mm, 12.52 mm, 12.53 mm, 12.54 mm, 12.55 mm, 12.56 mm, 12.57 mm, 12.58 mm, 12.59 mm, 12.6 mm, 12.61 mm, 12.62 mm, 12.63 mm, 12.64 mm, 12.65 mm, 12.66 mm, 12.67 mm, 12.68 mm, 12.69 mm, 12.7 mm, 12.71 mm, 12.72 mm, 12.73 mm, 12.74 mm, 12.75 mm, 12.76 mm, 12.77 mm, 12.78 mm, 12.79 mm, 12.8 mm, 12.81 mm, 12.82 mm, 12.83 mm, 12.84 mm, 12.85 mm, 12.86 mm, 12.87 mm, 12.88 mm, 12.89 mm, 12.9 mm, 12.91 mm, 12.92 mm, 12.93 mm, 12.94 mm, 12.95 mm, 12.96 mm, 12.97 mm, 12.98 mm, 12.99 mm, or 13 mm, and (iii) a height or thickness of approximately 5 mm, 5.01 mm, 5.02 mm, 5.03 mm, 5.04 mm, 5.05 mm, 5.06 mm, 5.07 mm, 5.08 mm, 5.09 mm, 5.1 mm, 5.11 mm, 5.12 mm, 5.13 mm, 5.14 mm, 5.15 mm, 5.16 mm, 5.17 mm, 5.18 mm, 5.19 mm, 5.2 mm, 5.21 mm, 5.22 mm, 5.23 mm, 5.24 mm, 5.25 mm, 5.26 mm, 5.27 mm, 5.28 mm, 5.29 mm, 5.3 mm, 5.31 mm, 5.32 mm, 5.33 mm, 5.34 mm, 5.35 mm, 5.36 mm, 5.37 mm, 5.38 mm, 5.39 mm, 5.4 mm, 5.41 mm, 5.42 mm, 5.43 mm, 5.44 mm, 5.45 mm, 5.46 mm, 5.47 mm, 5.48 mm, 5.49 mm, 5.5 mm, 5.51 mm, 5.52 mm, 5.53 mm, 5.54 mm, 5.55 mm, 5.56 mm, 5.57 mm, 5.58 mm, 5.59 mm, 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, 5.8 mm, 5.81 mm, 5.82 mm, 5.83 mm, 5.84 mm, 5.85 mm, 5.86 mm, 5.87 mm, 5.88 mm, 5.89 mm, 5.9 mm, 5.91 mm, 5.92 mm, 5.93 mm, 5.94 mm, 5.95 mm, 5.96 mm, 5.97 mm, 5.98 mm, 5.99 mm, or 6 mm. In yet another embodiment, the pharmaceutical composition may have (i) a length of approximately 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, or 19.3 mm as measured on the major axis, (ii) a width of approximately 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, or 12.5 mm, and (iii) a height or thickness of approximately 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, or 5.8 mm.

In additional embodiments, the pharmaceutical composition may expand upon immersion in fluid to have (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, or 21 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, or 14 mm within about 5 minutes of immersion in fluid. In other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21

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mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, or 22 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 10 minutes to about 15 minutes of immersion in fluid. In still other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 1 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, or 22.5 mm; and (ii) a width of about 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 20 minutes to about 25 minutes of immersion in fluid. In additional embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, or 23 mm; and (ii) a width of about 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 30 minutes to about 35 minutes of immersion in fluid. In still other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 18 mm, 18.1 mm, 18.2 mm, 18.3 mm, 18.4 mm, 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2 mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height or thickness of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 50 minutes to about 55 minutes of immersion in fluid. In yet another embodiment, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8

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16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, or 20% within about 60 minutes of immersion in fluid.

In a further embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 10 minutes of immersion in fluid. In still another embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 15 minutes of immersion in fluid. In yet another embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 20 minutes of immersion in fluid. In a further embodiment, the width of the pharmaceutical composition increases by about 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, or 24% within about 30 minutes of immersion in fluid. In another embodiment, the width of the pharmaceutical composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 45 minutes of immersion in fluid. In yet another embodiment, the width of the pharmaceutical composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 55 minutes of immersion in fluid. In still another embodiment, the width of the pharmaceutical composition increases by about 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 60 minutes of immersion in fluid.

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24.5%, 24.75%, 25%, 25.25%, 25.5%, 25.75%, or 26% within about 60 minutes of immersion in fluid.

The pharmaceutical composition disclosed herein includes one or more dosage forms that are designed to achieve the therapeutic concentrations of the active ingredients. In some embodiments, therefore, a therapeutically effective dose of the pharmaceutical composition may comprise one dosage form. In other embodiments, a therapeutically effective dose of the pharmaceutical composition may comprise two dosage forms. In additional embodiments, a therapeutically effective dose of the pharmaceutical composition may comprise three or more dosage forms.

(d) Abuse and Tamper Resistant Properties of the Composition

Extended release pain medications have provided many benefits to patients in the management of their chronic pain by providing a sustained release over time of a larger quantity of drug than is typically contained in an immediate release formulation. Consequently, these dosage forms (especially if they contain opioids) are attractive targets for drug abusers looking to defeat the extended release formulation to allow immediate bolus administration or "dose-dumping" of the entire drug contents of the dosage form.

Dosage forms of the pharmaceutical composition disclosed herein may be more resistant to crushing, grinding, pulverizing, or other common means used to produce a powder than an immediate release product. Accordingly, some embodiment forms are tamper resistant and less prone to abuse or misuse. For example, certain embodiments may not be crushed into a powder and snorted. Additionally, some embodiments comprising an extended release polymer may not be crushed, mixed with an aqueous solution, and injected (i.e., the resultant mixture becomes extremely viscous and cannot be drawn into a syringe).

For example, dosage forms of the pharmaceutical composition disclosed herein form a pasty semi-solid mixture when dissolved. Thus, the pharmaceutical composition is difficult to draw into a syringe and inject intravenously. The yield of active pharmaceutical ingredient(s) obtained from the pharmaceutical composition is also low (less than 20%).

Further, dosage forms of the pharmaceutical composition disclosed herein cannot easily be snorted. In order for a drug abuser to successfully snort a drug obtained from a dosage form, he must prepare a crushed, finely divided powder form of the dosage form for insufflating the powder into the nasal cavity. However, the pharmaceutical compositions disclosed herein form a clumpy, solid mass and do not allow acceptable absorption through the nasal tissue.

Dosage forms of the pharmaceutical composition disclosed herein also do not allow "dose dumping" caused by the deliberate introduction of alcohol into a drug abuser's stomach which accelerates the release of active ingredient(s) from the time-release formulation. The pharmaceutical compositions disclosed herein are resistant to the accelerated release of active ingredient(s).

In addition, dosage forms of the pharmaceutical composition disclosed herein do not allow for "free basing." Successful free basing by a drug abuser requires the generation of a salt free form of the active pharmaceutical ingredient(s). This requires physical and chemical manipulation to release the active pharmaceutical ingredient(s) from its salt(s) and selective extraction from other matrix excipients. The pharmaceutical composition disclosed herein cannot be easily manipulated to generate a free base preparation.

Moreover, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the average molecular weight of the extended

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release polymer used in the pharmaceutical composition. In another embodiment, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the amount of the extended release polymer used in the pharmaceutical composition.

In further embodiments, the solid oral dosage forms of the pharmaceutical compositions disclosed herein exhibit substantial differences in the release profiles of oxycodone and acetaminophen when the dosage forms are crushed or ground. Indeed, the intact solid oral dosage forms surprisingly exhibit a higher release rate of both active ingredients than one that is crushed or ground. This suggests that upon grinding or crushing the solid oral dosage forms disclosed herein, the immediate release portion and extended release portion of the dosage form combine, and the hydration and swelling of the polymer(s) in the extended release portion of the dosage form retards the release of the oxycodone and acetaminophen in the immediate release portion. Hence the incorporation of the ground or crushed components from the immediate release portion into a mixture with the ground or crushed components of the extended release portion causes the pharmaceutical composition to lose its immediate release characteristics. This feature may effectively negate a drug abuser's purpose for crushing the solid oral dosage form in the first place—to obtain an early onset of analgesia. Thus, this is an unexpected tamper resistant property of the pharmaceutical compositions disclosed herein.

In another embodiment, as the amount of oxycodone in the pharmaceutical composition increases, so does the duration of gastric retention after administration to a subject. Consequently, if a subject either intentionally or accidentally ingests a larger dose of the pharmaceutical composition than prescribed, the pharmaceutical composition will be retained in the stomach for a longer time period than an IR or traditional ER pharmaceutical composition, thereby giving a medical provider additional time to perform gastric lavage, induce vomiting, or administer activated charcoal to prevent the body from absorbing the oxycodone. In a further embodiment, the pharmaceutical composition provides a medical provider with about an additional 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 2.0 hours, 2.25 hours, 2.5 hours, 2.75 hours, 3.0 hours, 3.25 hours, 3.5 hours, 3.75 hours, or 4 hours in which to prevent the absorption of oxycodone in the subject. In another embodiment, the pharmaceutical composition provides a medical provider with sufficient time to treat a subject who has overdosed on oxycodone so that death, difficulty breathing, cardiac arrest, and limp muscles do not occur in the subject.

In yet another embodiment, if vomiting is induced or naturally occurs as a result of an increased dose of oxycodone, the entire pharmaceutical composition is expelled from the subject. Thus, toxic concentrations of the oxycodone due to absorption into the subject's blood are prevented by removing the further release of oxycodone. In still another embodiment, if vomiting is induced or naturally occurs as a result of the increased dose of oxycodone about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the pharmaceutical composition is expelled from the subject. In yet another embodiment, if vomiting is induced or naturally occurs within about 30 minutes to about 60 minutes after ingestion of the increased dose of oxycodone about 50% to about 65% of the oxycodone dose is expelled from the subject.

(e) In Vitro Release Properties of the Composition

The in vitro release rates of oxycodone and acetaminophen from the pharmaceutical compositions disclosed herein may

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be measured in 900 mL of 0.1N HCl using a USP type II paddle apparatus and at a paddle speed of either about 100 rpm or 150 rpm and a constant temperature of 37° C.

In one embodiment, the at least one immediate release portion of the composition may have in vitro release rates of oxycodone and acetaminophen as follows: more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes, or essentially 100% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes. In another embodiment, more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 minutes. In yet another embodiment, essentially 100% of the oxycodone and/or acetaminophen present in the at least one immediate release portion may be released within about 5 minutes.

In one embodiment, the at least one extended release portion of the composition may have in vitro release rates of oxycodone as follows: from about 1% to about 20% of the oxycodone present in the at least one extended release portion may be released within about 15 minutes, from about 35% to about 55% of the oxycodone present in the at least one extended release portion may be released within about 2 hours, from about 65% to about 85% of the oxycodone present in the at least one extended release portion may be released within about 4 hours, and at least about 90% of the oxycodone present in the at least one extended release portion may be released within about 8 hours.

In yet another embodiment, the at least one extended release portion may have in vitro release rates of oxycodone as follows: from about 1% to about 10% of the oxycodone present in the at least one extended release portion may be released within about 15 minutes, from about 40% to about 50% of the oxycodone present in the at least one extended release portion may be released within about 2 hours, from about 70% to about 80% of the oxycodone present in the at least one extended release portion may be released within about 4 hours, and from about 90% to about 100% of the oxycodone present in the at least one extended release portion may be released within about 8 hours.

In one embodiment, the at least one extended release portion may have in vitro release rates of acetaminophen as follows: from about 1% to about 15% of the acetaminophen present in the at least one extended release portion may be released within about 15 minutes, from about 25% to about 40% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 50% to about 65% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 80% to about 95% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

In another embodiment, the at least one extended release portion of the composition may have in vitro release rates of acetaminophen as follows: from about 1% to about 5% of the acetaminophen present in the at least one extended release portion may be released within about 15 minutes, from about 25% to about 35% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 55% to about 65% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 80% to about 90% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

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In one embodiment, the in vitro release rates of oxycodone from the composition may be as follows: about 25% to about 35% of oxycodone may be released from the composition within about 15 minutes, from about 50% to about 65% of oxycodone may be released from the composition in about 2 hours, from about 70% to about 85% of oxycodone may be released from the composition within about 4 hours, and from about 90% to about 100% of oxycodone may be released from the composition within about 8 hours.

In another embodiment, the pharmaceutical composition disclosed herein may have in vitro release rates of oxycodone as follows: about 25% to about 30% of oxycodone may be released from the pharmaceutical composition within about 15 minutes, from about 50% to about 60% of oxycodone may be released from the pharmaceutical composition within about 2 hours, from about 70% to about 80% of oxycodone may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 95% of oxycodone may be released from the pharmaceutical composition within about 8 hours.

In one embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: from about 50% to about 55% of acetaminophen may be released from the composition in about 15 minutes, from about 60% to about 75% of acetaminophen may be released from the composition in about 2 hours, from about 75% to about 85% of acetaminophen may be released from the composition in about 4 hours, and from about 90% to about 100% of acetaminophen may be released from the composition in about 8 hours.

In another embodiment, the in vitro release rates of acetaminophen from the pharmaceutical composition disclosed herein may be as follows: from about 50% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes, from about 60% to about 70% of acetaminophen may be released from the pharmaceutical composition within about 2 hours, from about 75% to about 85% of acetaminophen may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 100% of acetaminophen may be released from the pharmaceutical composition within about 8 hours.

Additionally, the in vitro release rates of oxycodone and acetaminophen from the pharmaceutical composition generally are not affected by low concentrations of ethanol (i.e., from about 5% v/v to about 20% v/v) when measured in 900 mL of 0.1 N HCl containing the desired percentage of ethanol using a USP type II paddle apparatus and at a paddle speed of about 150 rpm and a constant temperature of 37° C. For example, from about 25% to about 35% of oxycodone and about 50% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes when measured in the presence of 5% to 20% ethanol, and from about 50% to about 65% of oxycodone and from about 60% to about 70% of acetaminophen may be released from the pharmaceutical composition within about 2 hours when measured in the presence of 5% to 20% ethanol.

The in vitro release rates of oxycodone and acetaminophen from the pharmaceutical compositions disclosed herein generally are reduced, however, in the presence of 40% ethanol. For example, from about 5% to about 15% of the oxycodone and from about 15% to about 25% of the acetaminophen may be released from the pharmaceutical composition within about 15 minutes when measured in the presence of 40% ethanol, and from about 35% to about 45% of oxycodone and from about 45% to about 55% of acetaminophen may be

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released from the pharmaceutical composition within about 2 hours when measured in the presence of 40% ethanol.

Stated another way, less oxycodone is extracted from the pharmaceutical composition by a solution of 0.1 N HCl and 40% ethanol than is extracted by a solution of 0.1 N HCl. In some embodiments, less than about 75% of the oxycodone that is released in the presence of 0.1 N HCl may be released in the presence of 0.1 N HCl containing 40% ethanol. In additional embodiments, less than about 70%, 65%, 60%, 55%, 50%, 45%, or 40% of the oxycodone that may be released in the presence of 0.1 N HCl may be released in the presence of 0.1 N HCl and 40% ethanol. For example, less than about 40% of the oxycodone that may be released in the presence of 0.1 N HCl in about 15 minutes may be released in the presence of 0.1 N HCl and 40% ethanol within about 15 minutes. In other embodiments, less than about 60% of the oxycodone that may be released in the presence of 0.1 N HCl in about 30 minutes may be released in the presence of 0.1 N HCl and 40% ethanol within about 30 minutes. In additional embodiments, less than about 75% of the oxycodone that may be released in the presence of 0.1 N HCl in about 2 hours may be released in the presence of 0.1 N HCl and 40% ethanol within about 2 hours.

(f) Stability Data for the Pharmaceutical Composition

In one embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in any amount up to and including, but no more than, about 100 ppm. In other embodiments, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.6 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In still another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm, 0.3 ppm, 0.4 ppm, 0.5 ppm, 0.6 ppm, 0.7 ppm, 0.8 ppm, 0.9 ppm, 1.0 ppm, 1.1 ppm, 1.2 ppm, 1.3 ppm, 1.4 ppm, 1.5 ppm, 1.6 ppm, 1.7 ppm, 1.8 ppm, 1.9 ppm, 2.0 ppm, 2.1 ppm, 2.2 ppm, 2.3 ppm, 2.4 ppm, 2.5 ppm, 2.6 ppm, 2.7 ppm, 2.8 ppm, 2.9 ppm, 3.0 ppm, 3.1 ppm, 3.2 ppm, 3.3 ppm, 3.4 ppm, 3.5 ppm, 3.6 ppm, 3.7 ppm, 3.8 ppm, 3.9 ppm, 4.0 ppm, 4.1 ppm, 4.2 ppm, 4.3 ppm, 4.4 ppm, 4.5 ppm, 4.6 ppm, 4.7 ppm, 4.8 ppm, 4.9 ppm, 5.0 ppm, 5.1 ppm, 5.2 ppm, 5.3 ppm, 5.4 ppm, 5.5 ppm, 5.6 ppm, 5.7 ppm, 5.8 ppm, 5.9 ppm, and 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in any amount up to and including about 0.5% by weight of the oxycodone. In other embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to 40° C. and at about 60% to 75% relative humidity. In yet another embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25°

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C. to 40° C. and at about 60% to 75% relative humidity. In additional embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, Related Substance A (i.e., C-Normorphinan-6-carboxylic acid, 4,5-epoxy-6,14-dihydroxy-3-methoxy-17-methyl-, (5 α ,6 α)-) may be present in the pharmaceutical composition as a degradation product of oxycodone in a maximum amount of about 0.5% by weight of the oxycodone. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet another embodiment, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition in any amount up to about 0.15% by weight of the acetaminophen. In another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In still another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.05% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In other embodiments, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, and 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

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In one embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in a maximum amount of about 0.2% by weight of the oxycodone. In other embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01% to about 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet another embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.05% to about 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In further embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, and 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, the total acetaminophen degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the acetaminophen. In other embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In further embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

In one embodiment, the total oxycodone degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the oxycodone. In further embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity. In yet other embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25° C. to about 40° C. and at about 60% to about 75% relative humidity.

(g) In Vivo and Pharmacokinetic Properties of the Pharmaceutical Composition

The pharmaceutical composition disclosed herein comprises at least one immediate release portion for immediate release of oxycodone and acetaminophen such that therapeutic plasma concentrations are quickly attained (e.g., within one hour) and the initial onset of action is achieved within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the

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composition upon oral administration to a subject. The pharmaceutical composition disclosed herein also comprises at least one extended release portion for sustained release of oxycodone and acetaminophen over an extended period of time, e.g., about 3 to about 12 hours, or about 4 to about 9 hours, or at least about 6 hours, or at least about 8 hours, to the upper gastrointestinal tract where acetaminophen, and potentially oxycodone, is best absorbed.

The pharmaceutical composition may be orally administered to a subject once in a 24 hour period (q.d. or once-daily), two times in a 24 hour period (b.i.d. or twice-daily), or three times in a 24 hour period (t.i.d. or three times daily). In one embodiment, the pharmaceutical composition may be orally administered to the subject twice a day (i.e., every 12 hours). The subject may be a mammal, and in certain embodiments, the subject may be a human.

In another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition. This first or loading dose may assist the subject in more quickly attaining steady state blood levels of the active drugs. In a further embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising about 22.5 mg of oxycodone and about 975 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 tablets, each tablet comprising about 11.25 mg of oxycodone and about 462.5 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 tablets, each tablet comprising about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 tablets, each tablet comprising about 5.625 mg of oxycodone and about 231.25 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 capsules, each capsule comprising about 11.25 mg of oxycodone and about 462.5 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 capsules, each capsules comprising about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 capsules, each capsules comprising about 5.625 mg of oxycodone and about 231.25 mg of acetaminophen.

Upon oral administration to a subject, the pharmaceutical composition disclosed herein may maintain a therapeutic blood plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hours to about 12 hours after administration of the composition. In another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 1 hour to about 12 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 2 hour to about 10 hours after administration of the composition. In yet another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 1 hour to about 10 hours after administration of the composition. In still another embodiment, the

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plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 0.75 hour to about 10 hours after administration of the composition.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} (peak plasma concentration) for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg. In another embodiment, the mean C_{max} for oxycodone may range from about 1.0 ng/mL/mg to about 1.5 ng/mL/mg. In an additional embodiment, the mean C_{max} for oxycodone may be 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, or 1.6 ng/mL/mg. Moreover, the mean C_{max} for oxycodone at steady state may range from about 1.5 ng/mL/mg to about 2.0 ng/mL/mg, from about 1.6 ng/mL/mg to about 1.95 ng/mL/mg, or from about 1.7 ng/mL/mg to about 1.85 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of oxycodone. Deconvolution of the pharmaceutical composition and the target plasma profiles can be done in WinNonLin (version 5.2, Pharsight Corp., Mountain View, Calif.). The results of such a deconvolution analysis for oxycodone is depicted in FIG. 23. The biphasic absorption of oxycodone may be characterized by an initial rapid absorption resulting in a first peak in plasma concentration between about 1 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours as a result of slower absorption taking place from the at least one extended release portion after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic increase in blood plasma concentrations of oxycodone may be characterized by a plasma concentration-time profile for oxycodone in which the slope of a line drawn between 0 hour and about 2 hours is greater than the slope of a line drawn between about 2 hours and about 5 hours. See FIG. 23.

This biphasic increase in oxycodone levels resulting from the composition has several benefits. For example, providing rapid but not too high concentrations of oxycodone for quick onset of analgesia followed by maintenance of oxycodone levels over an extended time period could prevent a human subject from developing liking or dependence (abuse) for oxycodone. Further fluctuations in the oxycodone plasma levels could also prevent development of tolerance at the active site. Thus, the biphasic increase in oxycodone levels helps to prevent this acute tolerance.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for oxycodone from about 9.0 ng·hr/mL/mg to about 18.5 ng·hr/mL/mg. In a further embodiment, the mean AUC for oxycodone may be from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg. In another embodiment, the mean AUC for oxycodone may be about 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, or 16.0 ng·hr/mL/mg. Additionally, the mean AUC for oxycodone at steady state may range from about 11.0 ng·hr/mL/mg to about 17.0 ng·hr/mL/mg, from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} (time to peak plasma concentration) for oxycodone from about 2.0 hours to about 7.0 hours. In an alternate embodiment, the median T_{max} for

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oxycodone may be from about 3.0 hours to about 6.0 hours. In another embodiment, the median T_{max} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 or 6.0 hours. Moreover, the median T_{max} for oxycodone at steady state may range from about 1.5 hours to about 3.5 hours, or from about 2 hours to about 3 hours.

In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median tlag for oxycodone from about 0 hours to about 0.5 hours. In an alternate embodiment, the median tlag for oxycodone may be from about 0 hours to about 0.25 hours.

Rates of absorption are often assessed by comparing standard pharmacokinetic parameters such as T_{max} and C_{max} . The extent of absorption is assessed by the AUC. A short T_{max} has been used to indicate rapid absorption. The U.S. FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (March 2003) and related publications (Chen et al, Clin. Pharmacokinet. 40(8):565-72, 2001) also recommends the use of partial AUC for some modified-release drugs (“MR drugs”), such as the pharmaceutical compositions disclosed herein. A partial AUC calculation may be used to measure early exposure to a drug, which may signify an initial onset of pain relief and/or to measure prolonged exposure of a drug in achieving sustained relief. Partial AUC calculations can also demonstrate whether two MR drugs are truly bioequivalent by comparing, for example, an early partial AUC, which will be associated with a drug’s response onset, and a late partial AUC, which will be associated with a drug’s sustained response. The parameters for compositions vary greatly between subjects. The parameters also vary depending on aspects of the study protocol such as the sampling scheduling, subject posture and general subject health. Values quoted in this specification are given as mean±standard deviation unless otherwise noted.

For partial AUC calculations, the standard linear trapezoidal summation over each time interval is used. The partial AUCs are calculated from the mean pharmacokinetic profile. For time 0 to 1 hour the partial AUC is $AUC_{(0-1hr)}$; for time 0 to 2 hours the partial AUC is $AUC_{(0-2hr)}$; for time 0-4 hours the partial AUC is $AUC_{(0-4hr)}$; for time 0 to 6 hour the partial AUC is $AUC_{(0-6hr)}$; for time 0 to 8 hours the partial AUC is $AUC_{(0-8hr)}$; and for time 0 to the last measurable time point (“x”) the partial AUC is $AUC_{(0-x hr)}$ where each partial AUC is calculated according to standard pharmaceutical industry pharmacokinetic calculation methodologies as given by:

hd $AUC_{(0-1hr)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 1 hour.

$AUC_{(0-2hr)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 2 hours.

$AUC_{(0-4hr)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 4 hours.

$AUC_{(0-6hr)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 6 hours.

hd $AUC_{(0-8hr)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 8 hours.

$AUC_{(0-t)hr}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the last measurable time point.

$AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$ —Area under the drug concentration-time curve calculated using linear trapezoidal

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summation from time zero to the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations (“2SD”) for the immediate release drug. The FDA has identified this calculation in association with an early onset of response for certain modified-release dosage forms, which show complex pharmacokinetic characteristics. (See supra March 2003 Guidance; Draft Guidance on Dexmethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (November 2011)).

$AUC_{((T_{max} \text{ of IR product}+2SD)-t)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations (“2SD”) for the immediate release drug to the last measurable time point. The FDA has identified this parameter in association with sustaining the response for modified-release dosage forms, which shows complex pharmacokinetic characteristics. (See March 2003 Guidance supra; Draft Guidance on Dexmethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (November 2011)).

$AUC_{(x-y)hr}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time “x” (e.g., any measurable time point, such as 8 hours) to time “y” (e.g., any other measurable time point later than “x”, such as 12 hours).

$AUC_{(0-\infty)}$ —Area under the drug concentration-time curve calculated using linear trapezoidal summation from time 0 to infinity.

Further, partial AUC may be calculated using trapezoidal summation from time T_{max} to time t (the last measured time point of plasma concentration profile).

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for oxycodone from about 0.10 ng·hr/mL/mg to about 0.45 ng·hr/mL/mg, from about 0.15 ng·hr/mL/mg to about 0.25 ng·hr/mL/mg, or from about 0.25 ng·hr/mL/mg to about 0.35 ng·hr/mL/mg. In another embodiment, the AUC_{0-1hr} for oxycodone may be about 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, or 0.45 ng·hr/mL/mg.

In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.65 ng·hr/mL/mg to about 1.35 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be about 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30 or 1.35 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for oxycodone from about 2.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, from about 2.5 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, or 4.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{T_{max}-t}$ for oxycodone from about 5.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, from about 8.0 ng·hr/mL/mg to about 10.5 ng·hr/mL/mg, or from about 10.5 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg. In another embodiment, the $AUC_{T_{max}-t}$ for oxycodone may be about 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0 or 16.0 ng·hr/mL/mg.

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In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$:

$$\text{oxycodone mean} \pm \text{SD} = 1.0 \text{ h} \pm 0.89 \text{ h}; T_{max} + 2SD = 2.8 \text{ hours}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-2.8)}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-2.8)}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(2.8-48)}$ for oxycodone after a single dose from about 7.5 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, from about 8.45 ng·hr/mL/mg to about 13.7 ng·hr/mL/mg, or from about 9.5 ng·hr/mL/mg to about 11.5 ng·hr/mL/mg. In another embodiment, the $AUC_{(2.8-48)}$ for oxycodone may be about 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, or 12.5 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$:

$$\text{oxycodone mean} \pm \text{SD} = 1.9 \text{ h} \pm 1.2 \text{ h}; T_{max} + 2SD = 4.3 \text{ hours}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-4.3)}$ for oxycodone after a single dose from about 1.5 ng·hr/mL/mg to about 5.5 ng·hr/mL/mg, from about 2.0 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, from about 2.5 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-4.3)}$ for oxycodone may be about 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, 3.5, 3.55, 3.6, 3.65, 3.7, 3.75, 3.8, 3.85, 3.9, 3.95, 4.0, 4.05, 4.1, 4.15, 4.2, 4.25, 4.3, 4.35, 4.4, 4.45, 4.5, 4.55, 4.6, 4.65, 4.7, 4.75, 4.8, 4.85, 4.9, 4.95, 5.0, 5.05, 5.1, 5.15, 5.2, 5.25, 5.3, 5.35, 5.4, 5.45, or 5.5 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(4.3-48)}$ for oxycodone after a single dose from about 5.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 13.5

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ng·hr/mL/mg, from about 9.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 9.5 ng·hr/mL/mg to about 11.5 ng·hr/mL/mg. In another embodiment, the $AUC_{(4.3-48)}$ for oxycodone may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject in a fasted state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 3% to about 33% of the AUC_{0-r} , from about 10% to about 27% of the AUC_{0-r} , or from about 15% to about 22% of the AUC_{0-r} . In another embodiment, the pharmaceutical composition, when orally administered to a subject in a fed state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 5% to about 35% of the AUC_{0-r} , from about 12% to about 30% of the AUC_{0-r} , or from about 15% to about 25% of the AUC_{0-r} .

In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may provide a mean half-life of oxycodone that ranges from about 3.5 hours to about 5.5 hours, or from about 4 hours to about 5 hours. In various embodiments, the mean half-life of oxycodone may be about 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, or 5.2 hours.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, produces a plasma profile characterized by an abuse quotient for oxycodone from about 3 to about 5. In other embodiments, the abuse quotient for oxycodone may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0.

Moreover, upon oral administration, the pharmaceutical composition disclosed herein may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 1 hour to about 6 hours after administration. In another embodiment, the pharmaceutical composition may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 0.75 hour to about 6.5 hours after administration. In yet another embodiment, the composition may maintain a plasma concentration of acetaminophen of at least about 1 mg/mL from about 0.5 hour to about 12 hours after administration.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg. In other embodiments, the mean C_{max} for acetaminophen may be from about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, or 11.0 ng/mL/mg. Moreover, the mean C_{max} for acetaminophen at steady state may range from about 6.0 ng/mL/mg to about 9.0 ng/mL/mg, from about 6.5 ng/mL/mg to about 8.5 ng/mL/mg, or from about 7.0 ng/mL/mg to about 8.0 ng/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of acetaminophen. The biphasic absorption of acetaminophen may be characterized by an initial rapid absorption resulting in first peak in plasma concentrations between about 0.5 hour and 2 hours, which contributes to the early onset on action, and a second peak in plasma concentrations between about 3 hours and 7

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hours after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic increase in blood plasma concentrations of acetaminophen is characterized by a plasma concentration-time profile for acetaminophen in which the slope of a line drawn between 0 hour and 2 hour is greater than the slope of a line drawn between about 2 hours and 5 hours. See FIG. 24.

This biphasic increase in acetaminophen levels resulting from the composition has several benefits. For example, the initial rapid rise in plasma levels produce quick onset of analgesia and the slower absorption provides maintenance of analgesia for an extended period of time.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for acetaminophen from about 35.0 ng·hr/mL/mg to about 80.0 ng·hr/mL/mg. In a further embodiment, the mean AUC for acetaminophen may range from about 35.0 ng·hr/mL/mg to about 60.0 ng·hr/mL/mg. In other embodiments, the mean AUC for acetaminophen may be about 35.0, 40.0, 45.0, 50.0, 55.0, 60.0, 65.0, 70.0, 75.0, or 80.0 ng·hr/mL/mg. Additionally, the mean AUC for acetaminophen at steady state may range from about 40.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg, from about 35.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 37.0 ng·hr/mL/mg to about 42.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} for acetaminophen from about 0.5 hours to about 6.0 hours. In another embodiment, the median T_{max} for acetaminophen may be from about 1.0 hour to about 5.0 hours. In a further embodiment, the median T_{max} for acetaminophen may range from about 0.5 hour to about 4.0 hours. In still another embodiment, the median T_{max} for acetaminophen may range from about 0.75 to about 1.5 hours. In other embodiments, the median T_{max} may be about 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 hours. Moreover, the median T_{max} for acetaminophen at steady state may range from about 0.5 hour to about 1.0 hour, or from about 0.5 hour to about 0.75 hour.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median tlag for acetaminophen from about 0 hour to about 0.5 hour. In an alternate embodiment, the median tlag for acetaminophen may be from about 0 hour to about 0.25 hour. In one embodiment, the median tlag for acetaminophen may be 0 hour. In another embodiment, the median tlag for acetaminophen may be 0.25 hour.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by various partial AUCs for acetaminophen. The partial AUCs for acetaminophen are calculated as described above for oxycodone. The pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for acetaminophen from about 1.25 ng·hr/mL/mg to about 3.25 ng·hr/mL/mg, from about 1.60 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 2.75 ng·hr/mL/mg. In another embodiment, the AUC_{0-1} for acetaminophen may be about 1.25, 1.30, 1.40, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, 2.30, 2.35, 2.40, 2.45, 2.50, 2.55, 2.60, 2.65, 2.70, 2.75, 2.80, 2.85, or 2.90 ng·hr/mL/mg.

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In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 4.25 ng·hr/mL/mg to about 8.75 ng·hr/mL/mg, from about 5.50 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 6.0 ng·hr/mL/mg to about 7.25 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen may be about 4.25, 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.50, 7.75 or 8.0 ng·hr/mL/mg.

In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for acetaminophen from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, from about 13.0 ng·hr/mL/mg to about 14.5 ng·hr/mL/mg, or from about 14.5 ng·hr/mL/mg to about 16.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for acetaminophen may be about 10.0, 11.0, 12.0, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, or 17.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{Tmax-t} for acetaminophen from about 20.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg, from about 23.5 ng·hr/mL/mg to about 36.0 ng·hr/mL/mg, or from about 29.0 ng·hr/mL/mg to about 31.0 ng·hr/mL/mg. In another embodiment, the AUC_{Tmax-t} for acetaminophen may be about 20.0, 21.0, 22.0, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5 or 36.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-(Tmax\ of\ IR\ product+2SD))}$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(Tmax\ of\ IR\ product+2SD))}$ for acetaminophen may be about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(Tmax\ of\ IR\ product+2SD))}$:

$$\text{acetaminophen mean} \pm \text{SD} = 0.596 \text{ h} \pm 0.529 \text{ h}; T_{max} + 2SD = 1.65 \text{ hour}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-1.7)}$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-1.7)}$ for acetaminophen may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(1.7-48)}$ for acetami-

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nophen after a single dose from about 25.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 31.5 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(1.7-48)}$ for acetaminophen may be about 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0 ng·hr/mL/mg.

In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product}+2SD))}$:

$$\text{acetaminophen mean} \pm SD = 1.48 \text{ h} \pm 0.875 \text{ h}; T_{max} + 2SD = 3.2 \text{ hour}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3.2)}$ for acetaminophen after a single dose from about 7.0 ng·hr/mL/mg to about 21.0 ng·hr/mL/mg, from about 9.0 ng·hr/mL/mg to about 18.0 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-3.2)}$ for acetaminophen may be about 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, or 21.0 ng·hr/mL/mg.

In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3.2-48)}$ for acetaminophen after a single dose from about 15.0 ng·hr/mL/mg to about 75.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, from about 27.5 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 30.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg. In another embodiment, the $AUC_{(3.2-48)}$ for acetaminophen may be about 15.0, 15.5, 16.0, 16.5, 17.0, 17.5, 18.0, 18.5, 19.0, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, 55.0, 55.5, 56.0, 56.5, 57.0, 57.5, 58.0, 58.5, 59.0, 59.5, 60.0, 60.5, 61.0, 61.5, 62.0, 62.5, 63.0, 63.5, 64.0, 64.5, 65.0, 65.5, 66.0, 66.5, 67.0, 67.5, 68.0, 68.5, 69.0, 69.5, 70.0, 70.5, 71.0, 71.5, 72.0, 72.5, 73.0, 73.5, 74.0, 74.5, or 75.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0 ng·hr/mL/mg to about 60.0 ng·hr/mL/mg, from about 30 ng·hr/mL/mg to about 50 ng·hr/mL/mg, from about 35 to about 45 ng·hr/mL/mg, or from about 37.5 ng·hr/mL/mg to about 42.5 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to

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a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0. In a further embodiment, at AUC_{0-12hr} between about 70%-95%, about 75%-92%, or about 77%-90% of the acetaminophen has been cleared. In still another embodiment, about 80% of the acetaminophen has been cleared.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15.0 ng·hr/mL/mg to about 55.0 ng·hr/mL/mg, from about 25.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 30.0 to about 40.0 ng·hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15, 16, 17, 18, 19, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, or 50.0 ng·hr/mL/mg.

In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 5.0 ng·hr/mL/mg to about 25.0 ng·hr/mL/mg, from about 7.5 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, or from about 10.0 ng·hr/mL/mg to about 15.0. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5 ng·hr/mL/mg to about 15.5 ng·hr/mL/mg, from about 2 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg, from about 3.5 ng·hr/mL/mg to about 10 ng·hr/mL/mg, or from about 4.5 ng·hr/mL/mg to about 6.5 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for acetaminophen from about 5 ng·hr/mL/mg to about 30 ng·hr/mL/mg, from

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about 10 ng·hr/mL/mg to about 20 ng·hr/mL/mg, or from about 13 ng·hr/mL/mg to about 17 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-3hr)}$ for acetaminophen from about 5.0, 6.0, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, or 20.0 ng·hr/mL/mg.

In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3-36hr)}$ acetaminophen from about 20 ng·hr/mL/mg to about 50 ng·hr/mL/mg, from about 20 ng·hr/mL/mg to about 40 ng·hr/mL/mg, or from about 25 ng·hr/mL/mg to about 35 ng·hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(3-36hr)}$ acetaminophen from about 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5, or 50 ng·hr/mL/mg.

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 50% to about 90% of the AUC_{0-r} , from about 55% to about 85% of the AUC_{0-r} , or from about 75% to about 85% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen that is about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84% or 85% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 40% to about 90% of the AUC_{0-r} , from about 55% to about 85% of the AUC_{0-r} , or from about 60% to about 75% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen of about 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen from about 10% to about 40% of the AUC_{0-r} , from about 15% to about 35% of the AUC_{0-r} , or from about 20% to about 30% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{12-36hr}$ for acetaminophen of about 10%, 12%, 14%, 16%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% of the AUC_{0-r} .

In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma

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profile characterized by an AUC_{8-12hr} for acetaminophen from about 5% to about 30% of the AUC_{0-r} , from about 7% to about 25% of the AUC_{0-r} , or from about 10% to about 20% of the AUC_{0-r} . In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen of about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of the AUC_{0-r} .

In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 3 hours to about 5 hours. In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 4 hours to about 5 hours. In various embodiments, the mean half-life of acetaminophen may be about 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, or 8 hours. In additional embodiments, the pharmaceutical composition, when orally administered to a subject, has a mean observed half-life of acetaminophen that is more than the mean half-life of commercially available immediate release acetaminophen products.

In another embodiment, upon administration of the pharmaceutical composition to a subject, the composition may provide at least about 4 hours to about 12 hours of drug delivery to the upper gastrointestinal tract, which includes the duodenum, jejunum, and ileum of the small intestine. In another embodiment, the composition may provide at least about 6 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 8 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 9 hours, or at least about 10 hours of drug delivery to the upper gastrointestinal tract.

In yet another embodiment, upon administration of the pharmaceutical composition to a subject, APAP undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to pre-systemic metabolism is referred to as the fraction absorbed and denoted "Fab." This is different from the fraction bioavailable "F," which is the fraction that reaches the systemic circulation after the metabolism in the gut and liver.

In another embodiment, 60-90% of the acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 60-85% of acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See FIG. 27. Greater than 50% absorption of acetaminophen in the upper gastrointestinal tract is beneficial to a human subject because acetaminophen is poorly absorbed in the stomach and well absorbed in the small intestine and particularly, the upper segment of the gastrointestinal tract. It is therefore critical that acetaminophen is available in upper small intestine for its absorption. In one embodiment acetaminophen is released in stomach and reaches quickly into upper part of the small intestine for the absorption to take place.

In another embodiment, when about 60% to about 75% of the acetaminophen is released from the dosage form in the stomach within 2 hours following oral administration, about

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10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 27), about 15% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 27), and about 5% to about 15% is absorbed in the ileum.

In another embodiment, when about 70% to about 90% of the acetaminophen is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 27), about 15% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 27), and about 5% to about 15% is absorbed in the ileum.

In yet another embodiment, when at least about 55% of the total amount of the acetaminophen is released from the dosage form in the stomach within 1 hour after oral administration and when at least about 60% of the acetaminophen is released in the stomach after 2 hours, about 15% to about 20% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 30% to about 37% is absorbed in the proximal jejunum, about 15% to about 18% is absorbed in the distal jejunum, and about 8% to about 10% is absorbed in the ileum.

In still another embodiment, upon administration of the pharmaceutical composition to a subject, the opioid undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to presystemic metabolism is referred to as the fraction absorbed and denoted "F_{ab}." In one embodiment, the opioid is oxycodone. This is different from the fraction bioavailable "F," which is the fraction that reaches the systemic circulation after metabolism in the gut and liver.

In a further embodiment, 70-95% of the oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 80-95% of oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See FIG. 28.

In one embodiment, the composition releases the opioid and other API in the stomach to optimize drug absorption in the duodenum and jejunum. For example, when about 25% to about 50% of oxycodone is released from the dosage form in the stomach within 1 hour following oral administration, about 10% to about 45% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 50% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 7% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 15% is absorbed in the ileum.

In another embodiment, when about 45% to about 65% of oxycodone is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 50% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 55% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 5% to about 25% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 15% is absorbed in the ileum.

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In another embodiment, when about 60% to about 85% of oxycodone is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 55% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 30% to about 60% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 10% to about 30% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 20% is absorbed in the ileum.

In yet another embodiment, when at least 25% of the total amount of the oxycodone is released from the dosage form in the stomach within 1 hour after oral administration and when at least 45% of the oxycodone is released in the stomach after 2 hours, about 30% to about 45% of the total amount of oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 37% to about 43% is absorbed in the proximal jejunum (noted as "jejunum 1" in FIG. 28), about 10% to about 15% is absorbed in the distal jejunum (noted as "jejunum 2" in FIG. 28), and about 2% to about 8% is absorbed in the ileum.

In another embodiment, about 90% to about 100% of the IR dose of acetaminophen is released within about 15 minutes, 30 minutes, 45 minutes or 60 minutes after oral administration. In one embodiment, the dosage form provides a dissolution profile wherein about 20% to about 65%, about 35% to about 55% or about 40% to about 50% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration. In one embodiment, not more than 50% of the ER dose of acetaminophen is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the ER dose of acetaminophen is released within about the first hour. In another embodiment, not more than 85% of the ER dose of acetaminophen is released within about 4 hours. In yet another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 60% is released after about 6 hours. In one embodiment, the ER dose of acetaminophen is released over a time period of about 6 to 12, about 8 to 10, or about 9 to 10 hours in vitro. In another embodiment, the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In another embodiment, at least 90% or 95% of the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro.

In one embodiment, the pharmaceutical compositions disclosed herein rapidly achieve therapeutic plasma drug levels of oxycodone and acetaminophen similar to an immediate release product, which provides an early onset of action within about the first 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes or 60 minutes after administration of the composition, but unlike an immediate release product, the pharmaceutical composition is able to maintain those therapeutic plasma drug levels of oxycodone and acetaminophen over an extended period of time (e.g., up to 12 hours). Currently, there is no pharmaceutical composition available comprising oxycodone and acetaminophen which is able to provide a patient with quick onset of analgesia and maintenance of analgesia for an extended period of time.

In yet another embodiment, upon average, within one hour of administration to a subject, the pharmaceutical composition achieves a C_{max} for acetaminophen. The C_{max} achieved by the pharmaceutical composition disclosed herein is comparable to the C_{max} obtained from a commercially-available

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immediate release product containing acetaminophen formulated at half the strength of the commercially-available immediate release product. The acetaminophen continues to be released from the pharmaceutical composition at a rate less than the clearance rate for the acetaminophen, so that the acetaminophen levels fall smoothly until all of the acetaminophen is absorbed. Stated another way, the acetaminophen released by the pharmaceutical composition is eliminated by the body faster than it is being absorbed. The absorption of the acetaminophen released from the pharmaceutical composition is complete in about 8 to about 10 hours so that for one half life of acetaminophen the blood supply reaching the subject's liver via the portal vein contains no additional amounts of acetaminophen beyond the amounts present in the subject's general circulation.

These additional amounts of acetaminophen delivered to the liver from the subject's portal vein are frequently caused by the absorption of acetaminophen in the subject's gastrointestinal tract. Indeed, blood from the subject's intestines passes through the liver and then on to the general circulation. When acetaminophen is undergoing absorption, blood containing acetaminophen from the absorption process passes through the subject's liver prior to entering the general circulation where the acetaminophen is diluted by the distribution and clearance processes. The metabolism of these higher acetaminophen concentrations in blood coming into the subject's liver is termed the "first pass effect." Hence, the absorption process for acetaminophen taxes a subject's metabolic systems in the liver due to these higher "first pass" concentrations. Once the absorption process is complete, the concentration of acetaminophen in the blood reaching the subject's liver through the portal vein will be the same concentration of acetaminophen as found in blood throughout the rest of the subject's body. Thus, the pharmaceutical compositions disclosed herein provide a C_{max} comparable to a commercially-available immediate-release acetaminophen product (dosed at half strength) while providing a less taxing burden on the subject's metabolic systems in the liver because the acetaminophen released by the pharmaceutical composition is eliminated by the subject's body faster than it is being absorbed. This results in decreased levels of acetaminophen in a subject's liver as compared to an immediate release dosage form of acetaminophen dosed every 6 hours.

(h) Exemplary Compositions

In one embodiment, the pharmaceutical composition for extended release of oxycodone and acetaminophen comprises at least one extended release portion comprising acetaminophen, oxycodone or a combination thereof, and at least one extended release component; and at least one immediate release portion comprising oxycodone, acetaminophen or combinations thereof. In yet another embodiment, the pharmaceutical composition comprises an immediate release portion comprising oxycodone and acetaminophen and an extended release portion comprising oxycodone, acetaminophen and an extended release component. In still yet another embodiment, the composition comprises two extended release portions, each comprising an extended release component and one of the oxycodone or the acetaminophen, and an immediate release portion comprising the oxycodone and the acetaminophen. In another embodiment, the composition comprises two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and two immediate release portions, each comprising one of oxycodone or acetaminophen. In one embodiment, the extended release component comprises at least one extended release polymer. In another one embodiment, the extended release polymer comprises a

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polyethylene oxide. The molecular weight of the polyethylene oxide may be from about 500,000 Daltons to about 10,000,000 Daltons.

In another embodiment, the pharmaceutical composition may comprise from about 5 mg to about 30 mg of oxycodone and from about 250 mg to about 1300 mg of acetaminophen. In one exemplary embodiment, the pharmaceutical composition may comprise about 15 mg of oxycodone and about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 15 mg of oxycodone and about 500 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 15 mg of oxycodone and about 325 mg of acetaminophen. In a further embodiment, the composition may comprise about 30 mg of oxycodone and about 500 mg of acetaminophen. In yet another exemplary embodiment, the pharmaceutical composition may comprise about 7.5 mg of oxycodone about 325 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of oxycodone about 325 mg of acetaminophen. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of oxycodone about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 30 mg of oxycodone and about 650 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 22.5 mg of oxycodone and about 925 mg of acetaminophen.

In a further embodiment, a single dosage form of the pharmaceutical composition disclosed herein (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as either two dosage forms (e.g., two tablets) of the composition formulated at half the strength, or three dosage forms (e.g., three tablets) of the composition formulated at a third of the strength. In yet another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen). In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 5 mg of oxycodone and about 216.7 mg of acetaminophen). In yet another embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet comprising 22.5 mg of oxycodone and 650 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet configuration totaling 30 mg of oxycodone and 650 mg of acetaminophen. In yet a further exemplary embodiment, a pharmaceutical composition comprising 21

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mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 10.5 mg of oxycodone and 325 mg of acetaminophen). In yet another exemplary embodiment, a pharmaceutical composition comprising 22.5 mg of oxycodone and 925 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen).

In yet another embodiment, the at least one extended release portion of the composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen in the composition and from about 70% to about 80% (w/w) of the total amount of oxycodone in the composition, whereas the at least one immediate release portion may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen in the composition and from about 20% to about 30% (w/w) of the total amount of oxycodone in the composition. In still another embodiment, the at least one extended release portion may comprise about 50% (w/w) of the total amount of acetaminophen in the composition and about 75% (w/w) of the total amount of oxycodone in the

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composition; and the at least one immediate release portion may comprise about 50% (w/w) of total amount of acetaminophen in the composition and about 25% (w/w) of the total amount of oxycodone in the composition.

In another embodiment, an extended release portion of the composition may comprise, by weight of such extended release portion, from about 30% to about 50% of the extended release polymer, from about 20% to about 40% of acetaminophen, and from about 0.5% to about 2% of oxycodone; and an immediate release portion may comprise, by weight of such immediate release portion, from about 70% to about 80% acetaminophen and from about 0.5% to about 1% of oxycodone.

In yet another embodiment, the pharmaceutical composition may comprise from about 7.5 mg to about 30 mg of oxycodone and from about 325 mg to about 650 mg of acetaminophen, wherein the at least one immediate release portion may comprise about 25% (w/w) of the total amount of oxycodone in the composition and about 50% (w/w) of the total amount of acetaminophen in the composition, and the at least one extended release portion may comprise about 75% (w/w) of the total amount of oxycodone in the composition, about 50% (w/w) of the total amount of acetaminophen in the composition, and about 35% to about 45%, by weight of the at least one extended release portion, of an extended release polymer comprising a polyethylene oxide.

Other exemplary formulations are set forth in Charts 1-2 below:

CHART 1

		Representative Oxycodone/Acetaminophen Formulations.									
		Formulation No.									
		1	2	3	4	5	6	7	8	9	10
Immediate	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
Release	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
Layer	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
Extended	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
Release	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
Layer	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N12K	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 1105	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
		Formulation No.									
		11	12	13	14	15	16	17	18	19	20
Immediate	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
Release	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
Layer	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20

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CHART 1-continued

Representative Oxycodone/Acetaminophen Formulations.											
Extended Release Layer	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8
	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N12K	—	—	252.4	—	290.3	—	248.2	279.2	175.2	—
	Polyox 1105	275.8	—	—	—	—	—	—	—	—	224.5
	Hydroxypropyl methyl cellulose	—	101.1	—	110.5	—	192.1	—	—	140.9	185.6
	Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
	Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2
Formulation No.											
		21	22	23	24	25	26	27	28	29	30
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
Extended Release Layer	Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30
	Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5
	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N60K	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 205	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
	Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5
	Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3
Formulation No.											
		31	32	33	34	35	36	37	38	39	40
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
	Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37
	Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8

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CHART 1-continued

Representative Oxycodone/Acetaminophen Formulations.											
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075
	Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
	Polyox N60K	—	45.5	249.9	24.3	282.0	49.8	200.1	240.1	186.8	—
	Polyox 205	268.4	—	53.6	70.2	—	—	36.3	10.4	—	259.3
	Hydroxypropyl methyl cellulose	—	90.5	—	65.4	—	192.1	—	—	127.3	142.0
Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8	
Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2	
Formulation No.											
Immediate Release Layer	APAP	185.3	175.0	180.0	160.4	200.0	193.4	118.8	162.5	139.0	150.0
	Oxycodone hydrochloride	1.100	1.75	2.00	2.50	1.25	1.00	2.75	1.875	1.75	1.875
	Microcrystalline cellulose	23.0	17.0	19.0	27.0	16.0	18.0	18.0	14.0	21.0	24.0
	Pregelatinized starch	0.05	0.15	0.25	0.10	0.05	0.30	0.20	0.25	0.15	0.20
	Citric Acid Anhydrous	0.08	0.08	0.08	0.11	0.11	0.14	0.07	0.13	0.15	0.17
	EDTA disodium salt, dihydrate	0.087	0.106	0.075	0.03	0.050	0.055	0.033	0.025	0.045	0.018
	Hydroxypropyl cellulose	14.1	17.8	—	—	17.3	—	16.7	16.1	21.5	—
	Hypromellose	2.5	—	3.2	—	—	—	—	—	8.9	19.5
	Hydroxypropyl methyl cellulose	—	—	21.7	18.3	—	19.3	—	—	—	3.0
	Croscarmellose sodium	10.0	11.0	11.5	11.5	13.0	14.5	14.5	12.5	14.0	12.5
Silicon dioxide	0.97	0.75	1.14	1.02	1.10	1.03	0.88	1.05	0.93	2.30	
Magnesium stearate	1.5	1.0	1.0	0.5	0.5	2.0	2.0	0.5	1.5	2.5	
Extended Release Layer	APAP	185.3	150.0	145.0	155.2	125.0	100.5	146.9	162.5	207.4	150.0
	Oxycodone hydrochloride	6.900	5.75	5.50	5.00	6.25	6.50	7.25	5.625	4.75	6.625
	Microcrystalline cellulose	175.4	180.0	302.2	275.0	214.8	250.0	245.7	203.6	288.3	200.5
	Pregelatinized starch	0.60	0.60	0.70	0.70	0.70	0.75	0.75	0.75	0.85	0.85
	Citric Acid Anhydrous	0.24	0.16	0.24	0.22	0.33	0.28	0.07	0.38	0.45	0.34
	EDTA disodium salt, dihydrate	0.160	0.085	0.095	0.055	0.130	0.065	0.065	0.075	0.130	0.125
	Hydroxypropyl cellulose	30.0	275.8	95.5	210.6	13.2	40.7	32.9	9.6	—	—
	Polyox N-750	292.8	—	—	—	287.7	—	—	—	155.5	—
	Polyox 301	—	—	244.2	—	—	—	275.5	321.8	—	189.2
	Hydroxypropyl methyl cellulose	—	103.2	—	134.2	—	182.2	—	—	155.5	210.2
Silicon Dioxide	1.8	1.3	1.5	2.3	2.4	3.0	3.5	3.6	2.0	2.5	
Magnesium Stearate	7.5	8.0	7.4	8.1	7.5	10.2	9.9	7.2	10.3	10.3	
Formulation No.											
Immediate Release Layer	APAP	300.0	150.0	200.0	150.0	100.0	160.0	190.0	75.0	90.0	125.0
	Oxycodone hydrochloride	2.00	1.00	1.50	3.50	2.75	1.25	1.25	2.50	1.75	3.00
	Microcrystalline cellulose	21.5	18.5	25.3	35.0	15.7	27.1	9.9	13.9	24.2	16.9
	Pregelatinized starch	0.03	0.30	0.25	0.27	0.08	0.35	0.75	0.09	0.15	0.26
	Citric Acid Anhydrous	0.12	0.08	0.09	0.16	0.07	0.24	0.14	0.26	0.15	0.20
	EDTA disodium salt, dihydrate	0.04	0.175	0.1	0.06	0.1	0.09	0.06	0.08	0.063	0.09
	Hydroxypropyl cellulose	—	21.5	1.8	9.8	14.8	—	20.8	19.2	25.4	—
	Hypromellose	2.5	—	—	—	—	—	—	—	10.3	22.5
	Hydroxypropyl methyl cellulose	16.3	11.4	17.5	8.7	—	29.3	—	—	—	4.4
	Croscarmellose sodium	6.8	11.0	12.8	7.9	19.0	9.6	13.3	15.6	15.1	14.7
Silicon dioxide	0.86	0.80	2.25	1.24	.95	1.34	0.80	1.66	0.79	2.37	
Magnesium stearate	1.75	1.0	0.75	0.6	0.5	2.5	1.9	0.8	1.2	2.8	
Extended Release Layer	APAP	150.0	150.0	125.0	75.0	100.0	165.0	135.0	225.0	210.0	150.0
	Oxycodone hydrochloride	8.00	6.50	6.00	6.50	3.25	6.25	6.25	5.00	6.25	5.50
	Microcrystalline cellulose	182.2	197.6	300.4	269.6	210.0	275.5	283.2	310.2	240.8	210.0
	Pregelatinized starch	0.75	0.73	0.46	0.89	0.55	0.78	0.55	0.65	0.67	0.64
	Citric Acid Anhydrous	0.25	0.36	0.38	0.34	0.37	0.23	0.14	0.40	0.70	0.70
	EDTA disodium salt, dihydrate	0.23	0.09	0.14	0.06	0.183	0.035	0.049	0.03	0.105	0.075

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CHART 1-continued

Representative Oxycodone/Acetaminophen Formulations.										
Hydroxypropyl cellulose	34.7	321.9	88.4	212.9	11.9	37.7	34.2	17.4	—	—
Polyox N-750	63.4	30.1	125.9	100.3	149.2	63.2	150.5	140.3	94.3	—
Polyox 301	210.4	—	175.8	60.7	175.8	—	160.5	149.7	100.8	194.6
Hydroxypropyl methyl cellulose	—	128.3	—	65.4	—	227.7	—	—	127.3	142.0
Silicon Dioxide	1.3	1.3	1.2	2.4	2.1	3.2	4.0	4.0	2.0	3.8
Magnesium Stearate	5.7	9.4	6.6	5.5	7.7	9.4	6.4	5.2	9.9	7.2

CHART 2

Additional Oxycodone/Acetaminophen Formulations.											
		61	62	63	64	65	66	67	68	69	70
Immediate Release Layer	APAP	250.0	250.0	250.0	250.0	250.0	250.0	325.0	325.0	162.5	162.5
	Oxycodone hydrochloride	3.75	3.75	3.75	7.5	7.5	7.5	3.75	3.75	2.5	3.75
	Microcrystalline cellulose	23.72	23.72	23.72	32.42	32.42	32.42	28.10	28.10	15.50	18.40
	Pregelatinized starch	0.50	0.50	0.50	1.00	1.00	1.00	0.50	0.50	0.33	0.50
	Citric Acid Anhydrous	0.25	0.25	0.25	0.50	0.50	0.50	0.25	0.25	0.17	0.25
	EDTA disodium salt, dihydrate	0.05	0.05	0.05	0.10	0.10	0.10	0.05	0.05	0.033	0.05
	Hydroxypropyl cellulose	25.23	25.23	25.23	26.43	26.43	26.43	32.24	32.23	16.32	16.72
	Croscarmellose sodium	19.21	19.21	19.21	20.13	20.13	20.13	12.09	25.087	12.70	13.01
	Silicon dioxide	1.63	1.63	1.63	1.70	1.70	1.70	2.09	2.09	1.06	1.08
	Magnesium stearate	0.81	0.81	0.81	0.85	0.85	0.85	1.045	1.045	0.53	0.54
Extended Release Layer	APAP	250.0	250.0	250.0	250.0	250.0	250.0	325.0	325.0	162.5	162.5
	Oxycodone hydrochloride	11.25	11.25	11.25	22.5	22.5	22.5	11.25	11.25	7.5	11.25
	Microcrystalline cellulose	175.24	103.74	103.74	159.62	88.12	88.12	23.85	23.85	201.02	195.80
	Pregelatinized starch	1.50	1.50	1.50	3.00	3.00	3.00	1.50	1.50	1.00	1.50
	Citric Acid Anhydrous	0.75	0.75	0.75	1.50	1.50	1.50	0.75	0.75	0.50	0.75
	EDTA disodium salt, dihydrate	0.15	0.15	0.15	0.30	0.30	0.30	0.15	0.15	0.10	0.15
	Hydroxypropyl cellulose	15.13	15.13	15.13	17.11	17.11	17.11	—	19.16	9.91	10.57
	Polyox 1105	250.25	321.75	—	250.25	321.75	—	321.02	321.02	321.75	321.75
	Polyox N60K	—	—	321.75	—	—	321.75	—	—	—	—
	Silicon Dioxide	3.58	3.58	3.58	3.58	3.58	3.58	3.57	3.57	3.58	3.58
	Magnesium Stearate	7.15	7.15	7.15	7.15	7.15	7.15	7.13	7.13	7.15	7.15

*All weights in mg.

III. Methods for Preparing Solid Dosage Forms of the Pharmaceutical Composition

Another aspect of the disclosure provides methods for preparing solid dosage forms of the pharmaceutical composition that provide extended release of oxycodone and acetaminophen. Solid dosage compositions in the form of tablets may be produced using any suitable method known in the art including but not limited to wet granulation, dry granulation, direct compression, and combinations thereof.

Granulation is a manufacturing process which increases the size and homogeneity of active pharmaceutical ingredients and excipients that comprise a solid dose composition. The granulation process, which is often referred to as agglomeration, changes important physical characteristics of the dry composition, with the aim of improving manufacturability and, thereby, product quality, as well as providing desired release kinetics. Wet granulation is by far the more prevalent agglomeration process utilized within the pharmaceutical industry. Most wet granulation procedures follow some basic steps; the active agent(s) and excipients are mixed together, and a binder solution is prepared and added to the powder mixture to form a wet mass. The moist particles are then dried and sized by milling or by screening through a sieve. In some cases, the wet granulation is "wet milled" or sized through screens before the drying step. The wet granulation process may be a high shear granulation process or a fluid bed granulation process. Several methods of granulation are described in co-pending application U.S. application Ser. No. 13/166,770, filed Jun. 22, 2011, which is incorporated herein by reference in its entirety.

After granulation and drying of the resultant particles, batches are characterized with respect to properties such as final Loss on Drying (LOD), bulk density, tap density, and particle size. Loss on Drying (LOD) typically is determined after each granulation using the Moisture Analyzer. Several 1 g samples may be taken and loaded into the moisture analyzer. The samples may be run for 5 minutes at a temperature of 105° C. In another embodiment, the samples may be run at 105° C. until there is no weight fluctuation in order to determine the LOD.

Bulk and tap densities may be determined as follows. A graduated cylinder is filled with a certain amount of material (e.g., 30-40 g or 82-88 g), and the volume recorded to determine the material bulk density. Tap density can be determined with a help of a Tap Density Tester by exposing the material to 100 taps per test and recording the new volume.

Particle size determination generally is performed immediately after granulation, after sieving through 20 mesh screen to remove agglomerates. Particle diameter may be determined with a sieve-type particle diameter distribution gauge using sieves with openings of 30, 40, 60, 80, 120, and 325 mesh. Fractions may be weighed on a Mettler balance to estimate size distribution. This provides determination of the quantitative ratio by particle diameter of composition comprising extended release particles. Sieve analysis according to standard United States Pharmacopoeia methods (e.g., USP-23 NF 18), may be done such as by using a Meinzer II Sieve Shaker.

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In one embodiment, the method for preparing dosage forms of the pharmaceutical composition may comprise wet granulating a first mixture comprising oxycodone, acetaminophen, and a binder to produce a first granulation mixture. The wet granulation process may be a fluid bed granulation process. In additional embodiments, the first mixture may further comprise at least one additional excipient selected from the group consisting of fillers, lubricants, antioxidants, chelating agents, and color agents. The first granulation mixture may be blended with an extended release polymer and one or more excipients, as listed above, to form at least one extended release portion of a dosage form. In certain embodiments, the extended release polymer may be a polyethylene oxide.

In another embodiment, the method further comprises wet granulating a second mixture comprising oxycodone, acetaminophen, and a binder to form a second granulation mixture. The wet granulation process may be a fluid bed granulation process. In some embodiments, the second mixture may further comprise at least one additional excipient selected from the group consisting of fillers, lubricants, disintegrants, antioxidants, chelating agents, and color agents. The second granulation mixture may be blended with one or more excipients, as listed above, to form an immediate release portion of a dosage form.

In an additional embodiment, the method may further comprise compressing the at least one extended release portion and the at least one immediate release portion into a tablet. The tablet may be a bilayer tablet. The tablet may be coated with a tablet coating.

In another embodiment, the method may comprise granulating via a high shear wet granulation process a mixture comprising oxycodone and at least one excipient to form oxycodone particles. The oxycodone particles may be dried at a suitable temperature. The oxycodone particles comprising oxycodone may be granulated via a fluid bed granulation process with acetaminophen, a binder, and an optional excipient to form the granulation mixture. The granulation mixture may be blended with an extended release polymer and at least one excipient to form an extended release portion of a solid dosage form.

In a further embodiment, the method may further comprise granulating via a fluid bed granulation process oxycodone particles comprising oxycodone with acetaminophen, a binder, and an optional excipient to form another granulation mixture. This granulation mixture may be blended with one or more excipients to form an immediate release portion of a solid dosage form.

In an additional embodiment, the method may further comprise compressing the at least one extended release portion comprising oxycodone particles and the at least one immediate release portion comprising oxycodone particles into a tablet. In one embodiment, the method comprises compressing one extended release portion comprising the oxycodone particles and one immediate release portion comprising the oxycodone particles into a bilayer tablet. The tablet may be coated with a tablet coating.

In another embodiment, wet granulation of either mixture may produce particles with a bulk density ranging from about 0.30 to 0.40 grams/milliliter (g/mL). In other aspects, the wet granulation may produce particles with a tap density ranging from about 0.35 g/mL to about 0.45 g/mL. In other embodiments, the wet granulation may produce particles, wherein at least about 50% of the particles have a size greater than 125 microns. In still other embodiments, the wet granulation may

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produce particles wherein about 20% to about 65% of the particles have a size greater than about 125 microns and less than about 250 microns.

Tablets generally are characterized with respect to disintegration and dissolution release profiles as well as tablet hardness, friability, and content uniformity.

In vitro dissolution profiles for the tablets may be determined using a USP Type II apparatus, with a paddle speed of either about 100 rpm or 150 rpm, in 0.1 N HCl, at 37° C. Samples of 5 ml at each time-point may be taken without media replacement at 0.08, 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hours, for example. In some embodiments, the dissolution profiles may be determined at varying pH values, such as at a pH of about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 or 6.5. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. The resulting cumulative dissolution profiles for the tablets are based upon a theoretical percent active added to the compositions.

A tablet preferably disintegrates before it dissolves. A disintegration tester measures the time it takes a tablet to break apart in solution. The tester suspends tablets in a solution bath for visual monitoring of the disintegration rate. Both the time to disintegration and the disintegration consistency of all tablets may be measured. The disintegration profile may be determined in a USP Disintegration Tester in 0.1 N HCl of pH 1.2. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. Samples, 1-5 ml at each time-point, may be taken, for example, without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profiles are based upon a theoretical percent active added to the pharmaceutical compositions.

After tablets are formed by compression, it is desired that the tablets have a strength of at least 9-25 Kiloponds (kp), or at least about 12-20 kp. A hardness tester generally is used to determine the load required to diametrically break the tablets (crushing strength) into two equal halves. The fracture force may be measured using a Venkel Tablet Hardness Tester, using standard USP protocols.

Friability is a well-known measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability properties are especially important during any transport of the dosage form as any fracturing of the final dosage form may result in a subject receiving less than the prescribed medication. Friability may be determined using a Roche Friability Drum according to standard USP guidelines which specifies the number of samples, the total number of drum revolutions, and the drum rpm to be used. Friability values of from 0.8 to 1.0% generally are regarded as constituting the upper limit of acceptability.

The prepared tablets generally are tested for content uniformity to determine if they meet the pharmaceutical requirement of an acceptance value of 15 or less. Each tablet may be placed in a solution of 60% methanol/40% isopropanol and stirred at room temperature until the tablet disintegrates. The solution containing the dissolved tablet may be further diluted in 90% water/10% isopropanol/0.1% heptafluorobutyric acid and generally is analyzed by HPLC.

IV. Method for Reducing the Risk of Acetaminophen-Induced Hepatic Damage

The present disclosure also provides methods for reducing the risk of acetaminophen-induced hepatic damage in a subject being treated for pain with a dosage regimen that comprises administering to the subject at least two consecutive doses of a pharmaceutical composition comprising oxycodone and acetaminophen. The method comprises administering a first dose of a pharmaceutical composition compris-

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ing at least one extended release portion comprising the acetaminophen, the oxycodone or a combination thereof, and an extended release component to the subject, wherein the composition maintains a therapeutic blood plasma concentration of oxycodone of at least 5 ng/mL from about 0.75 hours to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration. The method further comprises administering a second dose of the pharmaceutical composition to the subject at about 12 hours after administration of the first dose.

Avoiding toxic intermediate formation is an important strategy in addressing product safety. Indeed, acetaminophen is absorbed from the stomach and small intestine and primarily metabolized by conjugation in the liver to nontoxic, water-soluble compounds that are eliminated in the urine. When the maximum daily dose ("MDD") is exceeded over a prolonged period, metabolism by conjugation becomes saturated, and excess acetaminophen is oxidatively metabolized by the CYP enzymes (CYP2E1, 1A2, 2A6, 3A4) to a reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). NAPQI has an extremely short half-life, and rapidly conjugates with available glutathione, which acts as a sulfhydryl donor. The reduced NAPQI is then renally excreted. The liver plays a central role in the turnover of glutathione in the body. Given that toxicity due to NAPQI formation occurs via necrosis of the liver following the formation of toxic adducts, minimizing glutathione depletion and enhancing glutathione regeneration in the liver is an important concern.

Human erythrocyte data resulting from hepatic turnover demonstrate a time-delayed response to redox and free radical insults via glutathione depletion and regeneration. The hepatic dynamics of glutathione formation and depletion in animal data using hepatic models can also be reviewed. In Swiss mice, the dynamics of glutathione depletion was investigated in detail for acetaminophen doses ranging from (100 mg/kg to 600 mg/kg) in work done by Brzezniczka and Piotrowski (1989). Under one embodiment of the present invention, the intended dosage for patients with acute pain is 1.3 g/day of acetaminophen. Assuming a subject's weight of 70 kg, this is 1.229×10 moles/kg/day in human subjects. In Swiss mice, 400 mg/kg and 600 mg/kg are 2.65×10^{-3} moles/kg/day and 3.97×10^{-3} moles/kg/day, respectively, resulting in a 22-fold and a 32-fold safety exposure ratio, as compared with human levels. The bioequivalence level is 95%. Brzezniczka and Piotrowski report that circulating hepatic GSH changes in mice began within 15 min after acetaminophen administration, and depletion followed a pattern that was strictly dose dependent, reaching a minimum GSH level 2 hrs after injection for the all dose groups, rebounding to initial levels between hours 8 and 12. Taken together, these results support the hypothesis that exposing subjects to the lower end of the therapeutic window of acetaminophen may provide benefit in terms of the patient's ability to regenerate physiologically protective levels of glutathione. Thus, the pharmaceutical formulations disclosed herein, which are designed to allow for a two hour break in acetaminophen exposure in each twelve hour exposure window allows for restorative hepatic regeneration of the subject's glutathione levels during that period when the acetaminophen concentrations are at their lowest or absent, while still preserving the considerable benefits of the potentiating effects of combination analgesia.

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As mentioned above, acetaminophen is primarily metabolized via conjugation reactions, e.g., glucuronidation and sulfation, in the liver to nontoxic, water-soluble compounds that are rapidly eliminated from the body. A small proportion of acetaminophen is metabolized by the cytochrome P450 system to the reactive metabolite, NAPQI. Generally, this toxic metabolite is rapidly detoxified by conjugation to glutathione to form a non-toxic metabolite that is renally excreted. However, if the conjugation pathways become saturated and more acetaminophen is metabolized via the cytochrome P450 pathway, the pool of available glutathione may become depleted. With insufficient glutathione to bind to and inactivate NAPQI, this toxic metabolite is able to react with the sulfhydryl groups of cellular proteins initiating a cascade of cellular damage, which may lead to liver necrosis, and, ultimately, liver failure.

The method disclosed herein addresses the problem of depleted stores of glutathione by providing a period of time during the later part of the dosing interval during which the release of acetaminophen is low because most of the acetaminophen has already been released from the composition. The period of time during which the release of acetaminophen is low is called the acetaminophen "time-off" period. As a consequence of this acetaminophen time-off period, the plasma levels of acetaminophen fall to sufficiently low levels such that the metabolic burden on the liver is reduced, thereby allowing the depleted stores of glutathione to be replenished via the continuous glutathione manufacturing pathway comprising the glutathione synthase pathway. Because the levels of glutathione are able to be restored before the next dose, the risk of acetaminophen-induced hepatic damage is significantly reduced.

Additionally, the acetaminophen time-off period provided by the compositions disclosed herein may provide an added and beneficial precaution for any subject undergoing acetaminophen therapy to avoid an inadvertent reduction in glutathione stores and any potential acetaminophen-induced hepatic damage. In particular, the acetaminophen time-off period provided by the compositions disclosed herein may be especially useful during chronic administration of analgesic compositions comprising acetaminophen. The subject may be at increased risk for developing acetaminophen-induced hepatic damage because of frequent and regular user of alcohol (i.e., ethanol), concurrent administration of acetaminophen from another source (e.g., an over-the-counter medication), poor diet, and/or compromised liver function.

In general, the compositions disclosed herein are formulated such that the rate of release of acetaminophen is high during the first several hours of the dosing interval and the rate of release of acetaminophen is low during the last several hours of the dosing interval. More specifically, the compositions are formulated to release from about 40% to about 65% of the acetaminophen in about 30 minutes, from about 55% to about 80% of the acetaminophen in about 2 hours, from about 65% to about 92% of the acetaminophen in about 4 hours, and from about 67% to about 95% of the acetaminophen in about 8 hours, wherein the dosing interval is about 12 hours. In another, the compositions are formulated to release from about 45% to about 60% of the acetaminophen in about 30 minutes, from about 57% to about 75% of the acetaminophen in about 2 hours, from about 67% to about 90% of the acetaminophen in about 4 hours, and from about 70% to about 95% of the acetaminophen in about 8 hours, wherein the dosing interval is about 12 hours. In yet another embodiment, during the final 4 hours of a 12 hour dosing interval, only about 5% of the acetaminophen remains to be released from the composition.

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The subject may be a mammal, and in certain embodiments, the subject may be a human. In various embodiments, the at least two consecutive doses of the analgesic composition may be administered to the subject at 8 hour intervals, 10 hour intervals, 12 hour intervals, 18 hour intervals, or 24 hour intervals.

The method for reducing the risk of acetaminophen-induced hepatic damage disclosed herein may further comprise administering additional doses of the pharmaceutical composition at regular dosing intervals, such as e.g., at 12 hour intervals. During the latter part of each dosing interval, therefore, the acetaminophen time-off period allows depleted stores of glutathione to be replenished, thereby reducing the risk of acetaminophen-induced hepatic damage in subjects being treated for pain with a composition comprising acetaminophen.

V. Method for Treating Pain

Also provided is a method for treating pain in a subject in need of such treatment with a pharmaceutical composition that comprises oxycodone and acetaminophen, wherein the method comprises administering an effective amount of any of the pharmaceutical compositions disclosed herein. The method comprises orally administering to the subject an effective amount of a pharmaceutical composition comprising at least one extended release portion comprising oxycodone, acetaminophen and combination thereof, and an extended release component, wherein the composition maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration.

In some embodiments, the subject may be suffering from or diagnosed with chronic pain. In yet another embodiment, the subject may be suffering from or diagnosed with acute pain. In still another embodiment, the subject may be suffering from or diagnosed with moderate to severe acute pain. In yet other embodiments, the subject may be suffering from or diagnosed with both chronic and acute pain. The subject may be a mammal, and in certain embodiments, the subject may be a human.

In one embodiment, the effective amount of a pharmaceutical composition may be 15 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 15 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 7.5 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 7.5 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 7.5 mg of oxycodone and 325 mg of acetaminophen may be administered. In yet another embodiment, the effective amount of a pharmaceutical composition may be 20 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 20 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 10 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 10 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 10 mg of oxycodone and 325 mg of acetaminophen may be administered. In

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still yet another embodiment, the effective amount of a pharmaceutical composition may be 30 mg of oxycodone and 650 mg of acetaminophen. For example, one solid dosage form comprising 30 mg of oxycodone and 650 mg of acetaminophen may be administered. Alternatively, two solid dosage forms with each comprising 15 mg of oxycodone and 325 mg of acetaminophen may be administered. In another embodiment, the effective amount of a pharmaceutical composition may be 15 mg of oxycodone and 325 mg of acetaminophen, wherein one solid dosage form comprising 15 mg of oxycodone and 325 mg of acetaminophen may be administered.

The dosing intervals of the effective amount of the pharmaceutical composition can and will vary. For example, an effective amount of the pharmaceutical composition may be administered once a day, twice a day, or three times a day. In another embodiment, an effective amount of the pharmaceutical composition may be administered twice a day.

In general, therapeutic plasma concentrations of oxycodone and acetaminophen are attained within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the first dose of the pharmaceutical composition. Accordingly, depending upon the severity of the pain, onset of analgesia may be attained within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition. Onset of analgesia may be measured by the double stopwatch method or other pain assessments as described in Example 12 below. Generally, analgesia or pain relief will be maintained throughout the duration of the dosing interval. For example, in one embodiment, analgesia or pain relief will be maintained for 12 hours. Upon administration of the next dose of the pharmaceutical composition, therefore, analgesia or pain relief may be maintained. Accordingly, analgesia or pain relief will be maintained as long as therapeutic amounts of the pharmaceutical composition are administered at regular dosing intervals. Moreover, pain relief may be managed such that no breakthrough episodes of pain occur.

In some embodiments, an effective amount of the pharmaceutical composition may be administered to a subject in a fed state. In general, a fed state is defined as having consumed food within about 30 min prior to administration of the pharmaceutical composition. The food may be a high fat meal, a low fat meal, a high calorie meal, or a low calorie meal. In other embodiments, an effective amount of the pharmaceutical composition may be administered to a subject in a fasted state. In general, a fasted state is defined as not having ingested food for at least 10 hours prior to administration of the pharmaceutical composition. In some embodiments, the pharmaceutical composition may be administered to a subject who has fasted for at least 10 hours prior to the first dose and who fasts for at least one hour prior to administration of subsequent doses. In other embodiments, the pharmaceutical composition may be administered to a subject who has fasted for at least 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours prior to administration of each dose.

The method of the present invention is useful for treating numerous pain states that are currently being treated with conventional immediate release compositions comprising acetaminophen and oxycodone. These and additional pain states include, by way of illustration and not limitation, headache pain, pain associated with migraine, neuropathic pain selected from the group consisting of diabetic neuropathy, HIV sensory neuropathy, post-herpetic neuralgia, post-thoracic

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cotomy pain, trigeminal neuralgia, radiculopathy, neuropathic pain associated with chemotherapy, reflex sympathetic dystrophy, back pain, peripheral neuropathy, entrapment neuropathy, phantom limb pain, and complex regional pain syndrome, dental pain, pain associated with a surgical procedure and or other medical intervention, bone cancer pain, joint pain associated with psoriatic arthritis, osteoarthritic pain, rheumatoid arthritic pain, juvenile chronic arthritis associated pain, juvenile idiopathic arthritis associated pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome) associated pain), pain associated with psoriatic arthritis, gout pain, pain associated with pseudogout (pyrophosphate arthritis), pain associated with systemic lupus erythematosus (SLE), pain associated with systemic sclerosis (scleroderma), pain associated with Behcet's disease, pain associated with relapsing polychondritis, pain associated with adult Still's disease, pain associated with transient regional osteoporosis, pain associated with neuropathic arthropathy, pain associated with sarcoidosis, arthritic pain, rheumatic pain, joint pain, osteoarthritic joint pain, rheumatoid arthritic joint pain, juvenile chronic arthritis associated joint pain, juvenile idiopathic arthritis associated joint pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome) associated joint pain), gout joint pain, joint pain associated with pseudogout (pyrophosphate arthritis), joint pain associated with systemic lupus erythematosus (SLE), joint pain associated with systemic sclerosis (scleroderma), joint pain associated with Behcet's disease, joint pain associated with relapsing polychondritis, joint pain associated with adult Still's disease, joint pain associated with transient regional osteoporosis, joint pain associated with neuropathic arthropathy, joint pain associated with sarcoidosis, arthritic joint pain, rheumatic joint pain, acute pain, acute joint pain, chronic pain, chronic joint pain, inflammatory pain, inflammatory joint pain, mechanical pain, mechanical joint pain, pain associated with the fibromyalgia syndrome (FMS), pain associated with polymyalgia rheumatica, monarticular joint pain, polyarticular joint pain, nociceptive pain, psychogenous pain, pain of unknown etiology, pain mediated by IL-6, IL-6 soluble receptor, or IL-6 receptor, pain associated with a surgical procedure in a patient with a clinical diagnosis of OA, pain like static allodynia, pain like dynamic allodynia, and/or pain associated with Crohn's disease.

Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

EXAMPLES

The following examples are included to demonstrate certain embodiments of the invention. Those of skill in the art should, however, in light of the present disclosure, appreciate that modifications can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth is to be interpreted as illustrative and not in a limiting sense.

Example 1

In Vitro Dissolution of Controlled-Release Bilayer Tablets

Control-release bilayer tablets were prepared containing 15 mg of oxycodone and 500 mg of acetaminophen (APAP),

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or 30 mg of oxycodone and 500 mg APAP. (See selected examples from Chart No. 2.) The ER layer contained 75% of the total amount of oxycodone in the tablet, 50% of the total amount of APAP in the tablet, and either 35% w/w POLYOX® 1105 (for fast release), 45% w/w POLYOX® 1105 (for medium release), or 45% w/w POLYOX® N60K (for slow release). The IR layer contained 25% of the total amount of oxycodone in the tablet and 50% of the total amount of APAP in the tablet.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel that contained 900 mL of (helium sparged) 0.1 N HCl that was heated to 37° C. ± 0.5° C. The mixture was stirred at 150 ± 6 rpm and the temperature was maintained at 37° C. ± 0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative release of oxycodone and APAP from 15 mg oxycodone/500 mg APAP tablets is presented in Table 1. Table 2 presents the cumulative release of oxycodone and APAP from 30 mg oxycodone/500 mg APAP (30/500) tablets. FIG. 1 presents the release profile of oxycodone from the 15/500 and 30/500 tablets. The dissolution profile of APAP from the 15/500 and 30/500 tablets is shown in FIG. 2. The release of oxycodone and APAP from the fast release and medium release tablets was essentially linear during the first half of the 12 hour time period but then plateaued during the last half of the 12 hour time period. The release of oxycodone and APAP from the slow release tablets was essentially linear during the entire 12 hour time period.

TABLE 1

Cumulative Release - 15 mg oxycodone/500 mg APAP Tablets						
Time (hr)	Oxycodone (%)			APAP (%)		
	Fast	Medium	Slow	Fast	Medium	Slow
0.25	27.56	25.70	25.68	54.78	53.06	53.01
0.5	34.33	31.31	30.39	57.55	55.73	54.89
1.0	—	40.85	37.81	—	60.03	58.03
2.0	59.88	55.67	49.50	71.42	68.16	63.27
4.0	83.46	77.94	67.43	86.17	81.55	72.31
6.0	97.48	92.12	80.53	96.19	91.62	79.97
8.0	101.26	99.26	90.20	100.16	96.96	86.06
12.0	101.57	101.23	99.36	100.10	99.16	94.41

TABLE 2

Cumulative Release - 30 mg oxycodone/500 mg APAP Tablets						
Time (hr)	Oxycodone (%)			APAP (%)		
	Fast	Medium	Slow	Fast	Medium	Slow
0.25	31.65	30.27	29.78	54.17	52.97	52.97
0.5	37.55	35.91	34.42	56.96	55.64	54.97
1.0	47.18	45.21	41.12	61.81	60.19	58.15
2.0	62.51	59.63	52.40	70.60	68.04	63.61
4.0	84.72	80.44	70.01	85.28	81.56	73.04
6.0	96.97	93.98	82.49	94.57	91.42	80.94
8.0	100.23	99.63	91.78	97.91	96.48	87.26
12.0	100.57	101.13	99.60	98.09	98.14	95.25

The cumulative in vitro release of oxycodone and APAP from 7.5 mg oxycodone/325 mg APAP medium release tablets is presented in Table 3. The ER layer of these tablets

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contained 5.625 mg of oxycodone, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105, and the IR layer contained 1.875 mg of oxycodone and 162.5 mg of APAP. (See selected example from Chart 1.) The dissolution profile was determined essentially as described above, except that samples were collected at 0.08 hour (~5 min) in addition to the later time points.

TABLE 3

Cumulative Release 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Oxycodone (%)		APAP (%)	
	Mean (%)	% RSD (6)	Mean (%)	% RSD (6)
0.08	26.6	4.3	49.0	3.4
0.25	31.5	4.2	51.3	3.1
0.5	37.5	2.7	53.8	2.9
1.0	45.9	1.6	58.2	2.5
2.0	60.1	1.7	66.0	2.3
4.0	81.4	1.1	78.7	1.7
6.0	95.4	1.4	88.4	1.9
8.0	101.8	0.9	93.9	1.4
12.0	103.2	1.2	94.9	1.1

FIG. 3 and FIG. 4 present the percentage of oxycodone and APAP, respectively, released from two different lots of 7.5/325 tablets as compared to 15/650 tablets (see Example 28 for the dissolution data of the 15 mg oxycodone/650 acetaminophen tablets). The dissolution profiles were similar among all the tablets.

The release of oxycodone and APAP from each layer was analyzed by determining the calculated release from the ER layer and actual release from the total composition. For this, the tablets contained 7.5 mg of oxycodone HCl and 325 mg of APAP (i.e., the ER layer contained 5.625 mg of oxycodone HCl, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105; and the IR layer contained 1.875 mg of oxycodone HCl and 162.5 mg of APAP). The dissolution profile was determined essentially as described above. The calculated cumulative release of oxycodone HCl from the ER layer and the total tablet is presented in Table 4, and the calculated cumulative release of APAP from the ER layer and the total tablet is presented in Table 5. These data show that essentially all of the 1.875 mg of oxycodone HCl in the IR layer was released within about 5 minutes and essentially all of the 162.5 mg of APAP in the IR layer was released within about 15 minutes.

TABLE 4

Split Release of Oxycodone 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
0.08	26.6	2.00	2.1	0.12
0.25	31.5	2.36	8.7	0.49
0.5	37.5	2.81	16.7	0.94
1.0	45.9	3.44	27.9	1.57
2.0	60.1	4.51	46.8	2.63
4.0	81.4	6.11	75.2	4.23
6.0	95.4	7.16	93.9	5.28
8.0	101.8	7.64	102.4	5.76
12.0	103.2	7.74	104.3	5.87

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TABLE 5

Split Release of APAP 7.5 mg oxycodone/325 mg APAP Tablets				
Time (hr)	Total (%)	Total (mg)	ER (%)	ER (mg)
0.08	49.0	159.25	0.0	0.00
0.25	51.3	166.73	2.6	4.22
0.5	53.8	174.85	7.6	12.35
1.0	58.2	189.15	16.4	26.65
2.0	66.0	214.50	32.0	52.00
4.0	78.7	255.78	57.4	93.28
6.0	88.4	287.30	76.8	124.80
8.0	93.9	305.18	87.8	142.68
12.0	94.9	308.43	89.8	145.93

Example 2

Clinical Pharmacokinetic Analysis of Controlled-Release 15 Mg Oxycodone/500 mg Acetaminophen Bilayer Tablets—Single Dose

An open-label, single dose, four-period crossover study was conducted to evaluate the pharmacokinetics (PK) and bioavailability of three controlled-release bilayer tablets comprising 15 mg oxycodone (OC) and 500 mg APAP as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen. The three controlled release formulations—fast, medium, and slow—are described above. (See selected examples from Chart No. 2.) One tablet of each of the controlled-release bilayer formulations was administered to the test subjects under fed conditions. One tablet of the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen was administered every 6 hours (Q6h) for two doses under fed conditions. The test subjects were about 40 normal, healthy male subjects between 21-45 years of age.

Subjects were randomly assigned to Treatments A, B, C, and D using a four-period, eight-sequence, crossover design as follows:

Treatment A: One (1) tablet of 15 mg OC/500 mg APAP, Fast Release administered orally under fed conditions.

Treatment B: One (1) tablet of 15 mg OC/500 mg APAP, Medium Release administered orally under fed conditions.

Treatment C: One (1) tablet of 15 mg OC/500 mg APAP, Slow Release administered orally under fed conditions.

Treatment D: One (1) tablet of a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg administered orally Q6h for two (2) doses under fed conditions.

The crossover design allowed for within-subject comparisons among the test formulations with differing release profiles. Subjects received each of the study drug treatments (A-D) separated by at least a 7-day interval between the start of each period at Hour 0. During each period, subjects remained in the clinical facility from the time of check-in (on the day prior to dosing) until discharge on Day 3 (after the 48 hour blood draw).

Physical examinations, electrocardiograms and clinical laboratory tests were performed at screening and at the conclusion of the study (or early termination). Vital sign measurements (including pulse oximetry) and adverse events were monitored during the study. Subjects were administered a 50 mg naltrexone tablet 12 hours prior to Hour 0 dosing, at Hour 0, and 12 hours post-dose to block the effects and

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potential risks of oxycodone. After a 10 hour overnight fast, subjects were served a standardized FDA high-fat breakfast to be consumed in 30 minutes or less prior to Hour 0 dosing for the first oral dosage. All subjects in each period were served a standardized meal to be consumed in 30 minutes or less prior to Hour 6. Only subjects randomized to Treatment D were administered the second oral dosage of the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen at Hour 6 in each period.

Blood was drawn at designated times for PK analysis. Samples (6 mL in pre-chilled vacuum blood collection tubes, containing K2EDTA as the anticoagulant) were taken pre-dose (up to 60 minutes prior to dose), 10 min, 20 min, 30 min, 40 min and 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36 and 48 hours post-dose. The collected plasma samples were analyzed for the active pharmaceutical ingredients (APIs), i.e., oxycodone and acetaminophen, using validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays.

The following PK parameters were calculated for oxycodone and acetaminophen using standard non-compartmental methods:

area under the plasma concentration curve to last quantifiable concentration $AUC_{(0-t)}$

area under the plasma concentration curve to infinite time

$AUC_{(0-inf)}$

maximum observed plasma concentration (C_{max})

time observed maximum plasma concentration (t_{max})

lag time (t_{lag})

apparent first-order terminal elimination rate constant (k_{el})

apparent plasma terminal elimination half-life ($t_{1/2}$)

Parametric general linear model (GLM) methodology was used in the analysis of all pharmacokinetic parameters. The SAS GLM procedure was used to perform analysis of variance (ANOVA) on each pharmacokinetic parameter with sequence, treatment, period, and subjects nested within sequences, as sources of variation. For each formulation, least squares means and the associated standard errors were obtained using the LSMEANS option. All treatment pairwise comparisons were performed, without adjustment for multiplicity. AUC and C_{max} were dose-adjusted for comparative purposes for acetaminophen and the commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen.

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The pharmacokinetic data for oxycodone and APAP are presented in Tables 6-8 and 9-11, respectively.

TABLE 6

Oxycodone Pharmacokinetics (15/500)						
Parameter	Fast Release Formulation				Commercially available immediate-release tablet	
	Mean	LSM	90% CI			
	(% CV)	Ratio	Lower	Upper	Mean (% CV)	
C_{max} (ng/mL)	18.803 (21)	82.92	78.02	88.12	22.428 (20)	
$C_{1\ hr}$ (ng/mL)	6.891 (77)	72.79	49.02	108.1	10.226 (65)	
$C_{2\ hr}^a$ (ng/mL)	12.355 (32)	80.74	71.2	91.56	14.94 (26)	
AUC_{0-t} (ng · hr/mL)	209.949 (26)	89.73	86.52	93.06	229.788 (22)	
AUC_{0-inf} (ng · hr/mL)	211.8 (25)	89.95	86.77	93.24	231.421 (22)	
$AUC_{0-1\ hr}$ (ng · hr/mL)	2.565 (104)	61.32	37.64	99.92	4.334 (80)	
$AUC_{0-2\ hr}^b$ (ng · hr/mL)	12.189 (53)	70.16	55.97	87.95	16.917 (46)	
$AUC_{0-4\ hr}^c$ (ng · hr/mL)	41.3 (29)	88.76	80.61	97.73	45.699 (24)	
T_{max} (hr)	4.954 (34)	na	na	na	7.954 (22)	
T_{lag} (hr)	0.31 (68)	na	na	na	0.219 (77)	
$T_{1/2}$ (hr)	4.584 (17)	na	na	na	4.495 (14)	
K_{el} (1/hr)	0.155 (16)	na	na	na	0.157 (13)	

^aConcentration at the median T_{max} for commercially-available immediate release tablet

^bAUC from zero to the median T_{max} for commercially-available immediate release tablet

^cAUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

TABLE 7

Oxycodone Pharmacokinetics (15/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	18.266 (25)	80.87	76.09	85.95	22.428 (20)
$C_{1\ hr}$ (ng/mL)	7.364 (81)	67.62	45.75	99.95	10.226 (65)
$C_{2\ hr}^a$ (ng/mL)	12.388 (45)	79.04	69.69	89.64	14.94 (26)
AUC_{0-t} (ng · hr/mL)	217.188 (23)	94.19	90.82	97.68	229.788 (22)
AUC_{0-inf} (ng · hr/mL)	218.545 (23)	94.09	90.77	97.54	231.421 (22)
$AUC_{0-1\ hr}$ (ng · hr/mL)	3.248 (118)	64.69	39.93	104.8	4.334 (80)
$AUC_{0-2\ hr}^b$ (ng · hr/mL)	13.124 (70)	71.74	57.22	89.96	16.917 (46)
$AUC_{0-4\ hr}^c$ (ng · hr/mL)	42.101 (43)	88.61	80.47	97.58	45.699 (24)

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TABLE 7-continued

Oxycodone Pharmacokinetics (15/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
T_{max} (hr)	5.31 (38)	na	na	na	7.954 (22)
T_{lag} (hr)	0.264 (64)	na	na	na	0.219 (77)
$T_{1/2}$ (hr)	4.557 (16)	na	na	na	4.495 (14)
K_{el} (1/hr)	0.156 (16)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

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TABLE 8

Oxycodone Pharmacokinetics (15/500)					
Parameter	Slow Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	17.403 (25)	76.75	72.21	81.58	22.428 (20)
C_{1hr} (ng/mL)	7.601 (79)	69.63	47.08	102.97	10.226 (65)
C_{2hr}^a (ng/mL)	11.237 (39)	73.55	64.84	83.43	14.94 (26)
AUC_{0-t} (ng · hr/mL)	222.096 (25)	95.62	92.2	99.18	229.788 (22)
AUC_{0-inf} (ng · hr/mL)	223.553 (25)	95.61	92.22	99.11	231.421 (22)
AUC_{0-1hr} (ng · hr/mL)	2.893 (112)	57.34	35.37	92.95	4.334 (80)
AUC_{0-2hr}^b (ng · hr/mL)	12.312 (66)	68.63	54.72	86.08	16.917 (46)
AUC_{0-4hr}^c (ng · hr/mL)	38.842 (35)	83.46	75.78	91.92	45.699 (24)
T_{max} (hr)	5.655 (27)	na	na	na	7.954 (22)
T_{lag} (hr)	0.299 (74)	na	na	na	0.219 (77)
$T_{1/2}$ (hr)	4.647 (19)	na	na	na	4.495 (14)
K_{el} (1/hr)	0.154 (18)	na	na	na	0.157 (13)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 9

Acetaminophen Pharmacokinetics (15/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet*
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2612 (26)	94.46	87.25	102.26	2721 (22)
C_{1hr} (ng/mL)	1627 (66)	113.22	84.91	150.98	1516 (58)
C_{2hr}^a (ng/mL)	2248 (30)	118.49	107.61	130.48	1841 (20)
AUC_{0-t} (ng · hr/mL)	21944 (27)	98.78	95.91	101.75	21962 (22)
AUC_{0-inf} (ng · hr/mL)	23090 (27)	98.73	95.85	101.7	23104 (21)
AUC_{0-1hr} (ng · hr/mL)	823 (96)	105.42	68.75	161.64	814 (82)
AUC_{0-2hr}^b (ng · hr/mL)	2761 (52)	106.73	86.55	131.62	2492 (47)
AUC_{0-4hr}^c (ng · hr/mL)	7006 (28)	119.91	110.42	130.2	5726 (22)
T_{max} (hr)	2.328 (58)	na	na	na	6.971 (34)
T_{lag} (hr)	0.276 (81)	na	na	na	0.219 (98)
$T_{1/2}$ (hr)	5.235 (35)	na	na	na	6.461 (66)
K_{el} (1/hr)	0.145 (28)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

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TABLE 10

Acetaminophen Pharmacokinetics (15/500)					
Parameter	Medium Release Formulation				Commercially- available immediate release tablet*
	Mean	LSM	90% CI		
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2720 (22)	99.19	91.61	107.39	2721 (22)
$C_{1\text{ hr}}$ (ng/mL)	1831 (54)	121.62	91.51	161.65	1516 (58)
$C_{2\text{ hr}}^a$ (ng/mL)	2170 (23)	116.69	105.96	128.51	1841 (20)
AUC_{0-t} (ng · hr/ mL)	22184 (22)	100.68	97.74	103.7	21962 (22)
AUC_{0-inf} (ng · hr/ mL)	23554 (22)	101.39	98.43	104.44	23104 (21)
$AUC_{0-1\text{ hr}}$ (ng · hr/ mL)	974 (85)	124.39	81.52	189.79	814 (82)
$AUC_{0-2\text{ hr}}^b$ (ng · hr/ mL)	2974 (47)	117.9	95.58	145.43	2492 (47)
$AUC_{0-4\text{ hr}}^c$ (ng · hr/ mL)	7122 (23)	123.98	114.17	134.64	5726 (22)
T_{max} (hr)	2.069 (66)	na	na	na	6.971 (34)
T_{lag} (hr)	0.218 (77)	na	na	na	0.219 (98)
$T_{1/2}$ (hr)	5.696 (33)	na	na	na	6.461 (66)
K_{el} (1/hr)	0.133 (29)	na	na	na	0.137 (39)

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

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TABLE 11

Acetaminophen Pharmacokinetics (15/500)							
5	Slow Release Formulation					Commercially-available immediate release tablet*	
	Parameter	Mean (% CV)	LSM Ratio	90% CI			Mean (% CV)
				Lower	Upper		
10	C_{max} (ng/mL)	2521 (18)	93.6	86.44	101.35	2721 (22)	
	$C_{1\text{ hr}}$ (ng/mL)	1766 (51)	126.26	94.96	167.87	1516 (58)	
15	$C_{2\text{ hr}}^a$ (ng/mL)	2113 (18)	116.18	105.48	127.96	1841 (20)	
	AUC_{0-t} (ng · hr/ mL)	21947 (25)	99.61	96.7	102.61	21962 (22)	
	AUC_{0-inf} (ng · hr/ mL)	23279 (25)	100.47	97.53	103.49	23104 (21)	
20	$AUC_{0-1\text{ hr}}$ (ng · hr/ mL)	872 (83)	115.25	75.49	175.95	814 (82)	
	$AUC_{0-2\text{ hr}}^b$ (ng · hr/ mL)	2811 (43)	116.49	94.42	143.73	2492 (47)	
25	$AUC_{0-4\text{ hr}}^c$ (ng · hr/ mL)	6828 (19)	120.68	111.11	131.07	5726 (22)	
	T_{max} (hr)	2.184 (59)	na	na	na	6.971 (34)	
30	T_{lag} (hr)	0.253 (86)	na	na	na	0.219 (98)	
	$T_{1/2}$ (hr)	5.366 (32)	na	na	na	6.461 (66)	
	K_{el} (1/hr)	0.141 (28)	na	na	na	0.137 (39)	

*Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median $T_{max} + 2SD$ for commercially-available immediate release tablet

40 The pharmacokinetic parameters for the medium release 15/500 formulation and the commercially-available immediate release tablet are shown in Table 12.

TABLE 12

Pharmacokinetic Profile (Mean ± SD) of Oxycodone/APAP versus commercially-available immediate release tablet (N = 29)						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max} (hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Oxycodone						
15 mg OC/500 mg APAP	18.3 ± 4.6	217 ± 49.2	219 ± 49.5	5.3 ± 2.0	0.156 ± 0.024	4.6 ± 0.7
Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP)	22.4 ± 4.5*	230 ± 49.8	231 ± 50.0	8.0 ± 1.7*	0.157 ± 0.020	4.5 ± 0.6
Acetaminophen						
15 mg OC/500 mg APAP	2720 ± 608	221184 ± 4804	23554 ± 5234	2.1 ± 1.4	0.133 ± 0.039	5.7 ± 1.9
Commercially-available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	2721 ± 584*	21962 ± 4772	23104 ± 4882	7.0 ± 2.4*	0.137 ± 0.054	6.5 ± 4.3

*Most values occurred after the second dose.

^aAUC and C_{max} dose-normalized to 500 mg for APAP.

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The oxycodone mean plasma concentration as a function of time after administration of 15/500 tablets is shown in Table 13 and FIG. 5. The APAP mean plasma concentration over time after administration of 15/500 tablets is shown in Table 14 and FIG. 6.

TABLE 13

Time Course of Oxycodone Plasma Concentration (ng/mL)								
Time (hr)	Mean Fast	SEM	Mean Medium	SEM	Mean Slow	SEM	Mean commercially-available immediate release tablet	SEM
0	0	0	0	0	0	0	0	0
0.17	0	0	0.13	0.11	0.06	0.02	0.03	0.03
0.33	0.65	0.29	1.08	0.44	0.93	0.41	1.16	0.36
0.5	2.09	0.55	2.98	0.95	2.55	0.96	4.03	0.9
0.67	3.74	0.91	5.29	1.25	4.15	1.1	7.04	0.93
1	6.89	0.98	7.36	1.11	7.6	1.24	10.23	1.11
2	12.36	0.74	12.39	1.04	11.24	0.73	14.94	0.81
3	14.77	0.82	14.73	0.91	13.35	0.53	14.84	0.62
4	16.33	0.8	16.1	0.82	15.12	0.44	12.95	0.58
5	16.28	0.67	15.89	0.81	15.83	0.41	10.58	0.8
6	17.4	0.72	16.43	0.81	15.76	0.41	9.1	0.67
6.5	16.59	0.64	15.89	0.72	15.22	0.96	10.76	0.7
7	15.28	0.58	14.83	0.69	14.49	1.43	16.84	0.69
8	14.02	0.6	14.29	0.64	13.77	0.85	19.7	0.7
9	13.13	0.57	13.39	0.55	13	0.78	19.08	0.65
10	11.9	0.64	12.52	0.53	11.92	0.68	16.63	0.57
12	8.86	0.6	9.59	0.49	10.04	0.59	10.88	0.53

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TABLE 14

Time Course of Acetaminophen Plasma Concentration (ng/mL)								
Time (hr)	Mean Fast	SEM	Mean Medium	SEM	Mean Slow	SEM	Mean commercially-available immediate release tablet	SEM
0	0	0	0	0	0	0	0	0
0.17	31	18	284	151	220	88	107	47
0.33	673	210	751	221	678	197	607	173
0.5	1216	266	1299	275	1133	248	1181	229
0.67	1624	301	1922	301	1647	252	1653	255
1	2116	258	2380	239	2296	217	1971	210
2	2922	160	2821	123	2747	93	2393	90
3	2736	129	2719	90	2636	94	2150	65
4	2643	120	2524	103	2424	110	1717	71
5	2376	112	2246	121	2130	118	1290	59
6	2263	100	2080	143	1965	107	1006	58
6.5	2068	93	1903	126	1774	102	1742	212
7	1830	80	1744	116	1644	98	2749	232
8	1577	81	1573	103	1495	93	2790	114
9	1416	79	1407	88	1330	80	2482	111
10	1286	82	1314	84	1198	71	1968	105
12	1069	89	1131	86	1089	66	1188	82

Example 3

Clinical Pharmacokinetic Analysis of
Controlled-Release 30 Mg Oxycodone/500 mg
Acetaminophen Bilayer Tablets—Single Dose

A single dose, four-period crossover study was conducted essentially as described in Example 2, except the controlled-release bilayer tablets contained 30 mg oxycodone and 500 mg APAP. (See selected examples from Chart No. 2.) Tables 15-17 and 18-20 present the PK data for oxycodone and APAP, respectively. The plasma concentrations of oxycodone and APAP are presented in FIG. 7 and FIG. 8, respectively.

TABLE 15

Oxycodone Pharmacokinetics (30/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	39.159 (28)	82.17	75.96	88.9	47.597 (26)
$C_{1\text{ hr}}$ (ng/mL)	20.462 (74)	77.25	54.37	109.76	25.911 (67)
$C_{2\text{ hr}}^a$ (ng/mL)	28.221 (39)	95.18	83.82	108.08	29.579 (32)
AUC_{0-4} (ng · hr/mL)	393.952 (30)	92.84	89.3	96.53	425.978 (29)
AUC_{0-inf} (ng · hr/mL)	396.135 (29)	92.4	88.94	95.99	430.196 (29)
$AUC_{0-1\text{ hr}}$ (ng · hr/mL)	9.106 (100)	71.09	46.05	109.76	11.55 (93)
$AUC_{0-2\text{ hr}}^b$ (ng · hr/mL)	33.448 (61)	82.59	67.9	100.46	39.295 (53)
$AUC_{0-4\text{ hr}}^c$ (ng · hr/mL)	96.47 (38)	101.27	91.51	112.06	93.706 (29)
$AUC_{4\text{ hr}-t}^d$	395.522 (29)	92.4	88.95	95.99	429.507 (29)
T_{max} (hr)	4.057 (51)	na	na	na	6.948 (33)
T_{lag} (hr)	0.213 (107)	na	na	na	0.184 (66)

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TABLE 15-continued

Oxycodone Pharmacokinetics (30/500)						
Parameter	Fast Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
T _{1/2} (hr)	4.398 (15)	na	na	na	4.32 (15)	
K _{el} (1/hr)	0.161 (15)	na	na	na	0.164 (16)	

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

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TABLE 16

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Oxycodone Pharmacokinetics (30/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	36.731 (30)	77.14	71.27	83.48	47.597 (26)
C_1 _{hr} (ng/mL)	19.758 (70)	86.12	60.48	122.62	25.911 (67)
C_2 _{hr} ^a (ng/mL)	27.655 (39)	93.53	82.31	106.28	29.579 (32)
AUC _{0-t} (ng · hr/mL)	396.026 (29)	94.17	90.55	97.92	425.978 (29)
AUC _{0-inf} (ng · hr/mL)	398.084 (29)	93.68	90.16	97.34	430.196 (29)
AUC _{0-1 hr} (ng · hr/mL)	8.988 (85)	93.06	60.12	144.04	11.55 (93)
AUC _{0-2 hr} ^b (ng · hr/mL)	32.695 (56)	86.02	70.64	104.74	39.295 (53)
AUC _{0-4 hr} ^c (ng · hr/mL)	91.998 (36)	98.13	88.63	108.65	93.706 (29)
AUC _{4 hr-t} ^d	397.436 (29)	93.68	90.16	97.34	429.507 (29)
T _{max} (hr)	4.523 (51)	na	na	na	6.948 (33)
T _{lag} (hr)	0.207 (95)	na	na	na	0.184 (66)
T _{1/2} (hr)	4.369 (14)	na	na	na	4.32 (15)
K _{el} (1/hr)	0.162 (14)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 17

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Oxycodone Pharmacokinetics (30/500)					
Parameter	Slow Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	32.976 (29)	68.96	63.74	74.6	47.597 (26)
$C_1\ hr$ (ng/mL)	17.897 (74)	73.61	52.01	104.18	25.911 (67)
$C_2\ hr^a$ (ng/mL)	23.183 (33)	78.42	69.06	89.05	29.579 (32)
AUC_{0-t} (ng · hr/mL)	399.623 (26)	94.5	90.9	98.25	425.978 (29)
AUC_{0-inf} (ng · hr/mL)	401.362 (26)	93.88	90.36	97.52	430.196 (29)
$AUC_{0-1\ hr}$ (ng · hr/mL)	7.643 (96)	69.93	45.52	107.44	11.55 (93)
$AUC_{0-2\ hr}^b$ (ng · hr/mL)	28.183 (59)	71.58	58.85	87.06	39.295 (53)
$AUC_{0-4\ hr}^c$ (ng · hr/mL)	82.171 (36)	86.17	77.87	95.35	93.706 (29)
$AUC_{4\ hr-t}^d$	400.56 (26)	93.85	90.34	97.49	429.507 (29)
T_{max} (hr)	3.96 (48)	na	na	na	6.948 (33)
T_{lag} (hr)	0.201 (78)	na	na	na	0.184 (66)
$T_{1/2}$ (hr)	4.418 (17)	na	na	na	4.32 (15)
K_{el} (1/hr)	0.161 (17)	na	na	na	0.164 (16)

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

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TABLE 18

Acetaminophen Pharmacokinetics (30/500)					
Parameter	Fast Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	3138 (32)	101.52	91.58	122.53	3085 (29)
$C_{1\text{ hr}}$ (ng/mL)	2163 (59)	130.98	101.04	169.78	1777 (59)
$C_{2\text{ hr}}^a$ (ng/mL)	2386 (32)	125.37	113.22	138.82	1892 (28)
AUC_{0-t} (ng · hr/mL)	21742 (26)	98.53	95.07	102.13	21897 (23)
AUC_{0-inf} (ng · hr/mL)	22798 (26)	99.02	95.5	102.66	22881 (23)
$AUC_{0-1\text{ hr}}$ (ng · hr/mL)	1260 (85)	122.71	85.05	177.03	1005 (80)
$AUC_{0-2\text{ hr}}^b$ (ng · hr/mL)	3534 (53)	120.52	100.69	144.26	2839 (48)
$AUC_{0-4\text{ hr}}^c$ (ng · hr/mL)	8038 (33)	130.54	119.98	142.02	6041 (27)
$AUC_{4\text{ hr}-t}^d$	14707 (32)	86.22	82.35	90.27	16720 (26)
T_{max} (hr)	1.908 (69)	na	na	na	5.615 (54)
T_{lag} (hr)	0.236 (106)	na	na	na	0.178 (90)
$T_{1/2}$ (hr)	4.798 (26)	na	na	na	5.3 (43)
K_{el} (1/hr)	0.153 (25)	na	na	na	0.152 (36)

* Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 19

Acetaminophen Pharmacokinetics (30/500)					
Parameter	Medium Release Formulation				Commercially-available immediate release tablet
	Mean	LSM	90% CI		Mean
	(% CV)	Ratio	Lower	Upper	(% CV)
C_{max} (ng/mL)	2940 (38)	93.8	84.57	104.03	3085 (29)
$C_{1\ hr}$ (ng/mL)	2161 (56)	139.29	107.29	180.84	1777 (59)
$C_{2\ hr}^a$ (ng/mL)	2349 (27)	125.86	113.61	139.44	1892 (28)
AUC_{0-4} (ng · hr/mL)	21822 (26)	99.42	95.9	103.06	21897 (23)
AUC_{0-inf} (ng · hr/mL)	23107 (26)	100.76	97.16	104.49	22881 (23)
$AUC_{0-1\ hr}$ (ng · hr/mL)	1342 (81)	155.89	107.81	225.4	1005 (80)

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TABLE 19-continued

Acetaminophen Pharmacokinetics (30/500)						
5	Medium Release Formulation				Commercially- available immediate release tablet	
	Mean	LSM	90% CI			Mean
	Parameter	(% CV)	Ratio	Lower		Upper
10	AUC _{0-2 hr} ^b	3596	129.14	107.79	154.73	2839
	(ng · hr/mL)	(52)				(48)
15	AUC _{0-4 hr} ^c	7880	130.08	119.51	141.59	6041
	(ng · hr/mL)	(32)				(27)
20	AUC _{4 hr-t} ^d	15040	88.93	84.92	93.13	16720
		(29)				(26)
25	T _{max}	1.724	na	na	na	5.615
	(hr)	(62)				(54)
25	T _{lag}	0.19	na	na	na	0.178
	(hr)	(114)				(90)
25	T _{1/2}	6.116	na	na	na	5.3
	(hr)	(63)				(43)
30	K _{el}	.0139	na	na	na	0.152
	(1/hr)	(37)				(36)
* Dose Normalized to 500 mg						
^a Concentration at the median T _{max} for commercially-available immediate release tablet						
^b AUC from zero the median T _{max} for commercially-available immediate release tablet						
^c AUC from the zero to the median T _{max} + 2SD for commercially-available immediate release tablet						

* Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

TABLE 20

40	Acetaminophen Pharmacokinetics (30/500)					Commercially-available immediate release tablet
45	Slow Release Formulation					
	Mean	LSM	90% CI		Mean	
	Parameter	(% CV)	Ratio	Lower	Upper	(% CV)
50	C_{max} (ng/mL)	2734 (33)	88.33	79.68	97.91	3085 (29)
	$C_{1\text{ hr}}$ (ng/mL)	1989 (53)	120.26	93.05	155.44	1777 (59)
	$C_{2\text{ hr}}^a$ (ng/mL)	2131 (25)	112.77	101.84	124.86	1892 (28)
55	AUC_{0-4} (ng · hr/mL)	21272 (23)	97.1	93.68	100.64	21897 (23)
	AUC_{0-inf} (ng · hr/mL)	22504 (22)	98.45	94.95	102.07	22881 (23)
	$AUC_{0-1\text{ hr}}$ (ng · hr/mL)	1092 (76)	120.91	84.15	173.72	1005 (80)
60	$AUC_{0-2\text{ hr}}^b$ (ng · hr/mL)	3152 (45)	112.74	94.19	134.94	2839 (48)
	$AUC_{0-4\text{ hr}}^b$ (ng · hr/mL)	7217 (26)	119.31	109.5	129.61	6041 (27)
	$AUC_{4\text{ hr}-t}^d$ (ng · hr/mL)	15227 (26)	90.59	86.52	94.85	16720 (26)
65	T_{max} (hr)	1.897 (56)	na	na	na	5.615 (54)
	T_{lag} (hr)	0.196 (79)	na	na	na	0.178 (90)

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TABLE 20-continued

Acetaminophen Pharmacokinetics (30/500)						
Parameter	Slow Release Formulation				Commercially-available immediate release tablet	
	Mean	LSM	90% CI			Mean
	(% CV)	Ratio	Lower	Upper		(% CV)
T _{1/2} (hr)	4.843 (27)	na	na	na	5.3 (43)	
K _{el} (1/hr)	0.152 (24)	na	na	na	0.152 (36)	

* Dose Normalized to 500 mg

^aConcentration at the median T_{max} for commercially-available immediate release tablet^bAUC from zero to the median T_{max} for commercially-available immediate release tablet^cAUC from the zero to the median T_{max} + 2SD for commercially-available immediate release tablet

The pharmacokinetic parameters for the medium release 30/500 formulation and the commercially-available immediate release tablet are shown in Table 21.

TABLE 21

Pharmacokinetic Profile (Mean ± SD) of Oxycodone/APAP versus Commercially-available immediate release tablet (N = 29)						
Dosage	C _{max} (ng/mL)	AUC _{0-t} (ng · hr/mL)	AUC _{0-inf} (ng · hr/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
Oxycodone						
30 mg OC/500 mg APAP	36.7 ± 10.9	396 ± 116	398 ± 115	4.5 ± 2.3	0.162 ± 0.023	4.4 ± 0.6
Commercially-available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	47.6 ± 12.3*	426 ± 125	430 ± 124	6.9 ± 2.3*	0.164 ± 0.026	4.3 ± 0.6
Acetaminophen						
30 mg OC/500 mg APAP	2940 ± 1105	21822 ± 5630	23107 ± 5927	1.7 ± 1.1	0.139 ± 0.052	6.1 ± 3.9
Commercially-available immediate release tablet ^a (7.5 mg OC/325 mg APAP)	3085 ± 899*	21897 ± 5125	22881 ± 5362	5.6 ± 3.0*	0.152 ± 0.055	5.3 ± 2.3

*Most values occurred after the second dose.

^aAUC and C_{max} dose-normalized to 30 mg for OC and 500 mg for APAP.

Example 4

Clinical Pharmacokinetic Analysis of Controlled-Release 15 Mg Oxycodone/650 mg Acetaminophen Bilayer Tablets—Single Dose

The following study evaluated the bioavailability, pharmacokinetics, dose-proportionality, and safety of 1 or 2 tablets of 15 mg of a composition comprising OC/650 mg APAP (1 dose) (see selected example from Chart No. 1) compared to 1 tablet of the commercially-available immediate release tablet under fed conditions. The ER layer contained 75% of the total amount of the oxycodone in the tablet, 50% of the total amount of APAP in the tablet, and 45% (w/w) POLYOX®

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1105. The IR layer contained 25% of the total amount of oxycodone in the tablet and 50% of the total amount of APAP. This study was conducted in 42 male and female healthy subjects.

PK parameters for oxycodone are presented in Table 22. Plasma concentrations of OC for the 1 tablet dosing configuration of 15/650 showed a median t_{lag} of 0.25 hours, while there was no lag time for plasma concentrations of OC for the 2 tablet dosing configuration of 15/650 and the commercially-available immediate release tablet under fed conditions. As illustrated in FIG. 9 demonstrating the plasma concentrations of oxycodone versus time of treatment (i.e., Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions; Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions; and Treatment C was one tablet of the commercially-available immediate release tablet (7.5 mg oxycodone/325 mg acetaminophen) administered orally every 6 hours for 2 doses under fed conditions). Plasma concentrations of OC

rose rapidly after administration of 15/650 formulation in a similar fashion to commercially-available immediate release tablet. Peak plasma levels of OC for the 15/650 tablets, however, were biphasic. Peak levels were observed at about 2-3 hours and about 6 hours for the 1 or 2 tablet dosing configuration of the 15/650 formulation. In contrast, the peak plasma level of OC for the commercially-available immediate release tablet was about 7-8 hours after the initial dose of the commercially-available immediate release tablet (~1-2 hr after the second dose). Mean plasma concentrations of OC from 15/650 formulations were detectable through 48 hours following all treatments and t_{1/2} was about 4 hours across all treatments.

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TABLE 22

Pharmacokinetic Parameter Estimates (Mean \pm SD) of Oxycodone Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet (N = 25)	17.68 (4.42)	199.60 (59.52)	201.6 (59.27)	3.00 (1.00-12.45)	0.25 (0.00-0.75)	4.18 (0.77)
Treatment A						
Two tablets (N = 25)	29.18 (6.53)	414.73 (109.87)	417.41 ^b (112.17)	5.00 (1.00-12.00)	0.00 (0.00-0.50)	4.11 ^b (0.67)
Treatment B						
Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP (N = 25) Treatment C	20.34 (4.81)	199.63 (60.53)	201.76 (60.24)	7.00 (0.50-9.00)	0.00 (0.00-1.00)	4.08 (0.64)

^a T_{max} and t_{lag} median (minimum-maximum)^bN = 24

PK parameters for APAP are presented in Table 23. Plasma concentrations of APAP for the 1 tablet dosing configuration of 15/650 showed a median t_{lag} of 0.25 hour, while there was no lag in the appearance of APAP in plasma for the 2 tablet dosing configuration of 15/650 and the commercially-available immediate release tablet. Plasma concentrations of APAP rose rapidly after administration of the 15/650 formulations, similar to that observed with RDL. (See FIG. 10). Peak plasma levels of APAP following administration of the 1 tablet and 2 tablet dosing configurations of 15/650 were observed at approximately 2 hours (with a shoulder peak at 5-6 hours) after dosing compared with 1 hour after the second dose of the commercially-available immediate release tablet. Mean plasma concentrations of APAP were detectable through 36 hours following all treatments and the mean $t_{1/2}$ was approximately 6 to 8 hours across treatment groups.

Example 5

Clinical Pharmacokinetic Analysis of
Controlled-Release 15 mg Oxycodone/650 mg
Acetaminophen Bilayer Tablets—Multiple Doses

The following study evaluated the steady state bioavailability, pharmacokinetics, and safety of a 15 mg OC/650 mg APAP composition administered (see selected example from Chart No. 2) orally as 1 tablet (Treatment A) or 2 tablets (Treatment B) every 12 hours (9 doses) compared to 2 tablets of the commercially-available immediate release tablet (2 \times 7.5 mg OC/325 mg APAP) (Treatment C) dosed every 6 hours for 4.5 days (18 doses) under fed conditions with 48 male and female subjects in equal distribution.

TABLE 23

Pharmacokinetic Parameter Estimates (Mean \pm SD) of APAP Following Administration of 15 mg Oxycodone/650 mg APAP versus Commercially-available immediate release tablet						
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng \cdot hr/mL)	AUC_{0-inf} (ng \cdot hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet (N = 25)	3822 (874)	30239 (5673)	32194 ^c (6437)	2.00 (0.50-4.00)	0.25 (0.00-1.00)	6.17 ^c (2.22)
Two tablets (N = 25)	6941 (1989)	64783 (15017)	67600 ^d (14655)	2.00 (0.50-5.00)	0.00 (0.00-0.50)	7.67 ^d (4.06)
Commercially- available immediate release tablet (7.5 mg OC/325 mg APAP (N = 25)	3629 (841)	30137 (6426)	30802 ^c (6697)	6.50 (0.50-9.00)	0.00 (0.00-1.00)	5.89 ^c (2.63)

^a T_{max} and t_{lag} median (minimum-maximum)^cN = 21^dN = 23

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The pharmacokinetic (PK) parameters of OC are presented in Table 24. The PK behavior of OC on Study Day 1 was similar to that observed in the single dose study (see Table 22). There was a slight lag (median tlag 0.25 hr) in the appearance of OC following the 1 tablet dose of 15 mg OC/650 mg APAP. No lag was observed following dosing with 2 tablets of 15 mg OC/650 mg APAP or the commercially-available immediate release tablet. Peak plasma levels were observed at 4 and 6 hours after administration of 1 and 2 tablets of the 15/650 formulation, respectively, and at 1.5 hours after the second dose of the commercially-available immediate release tablet. (See FIG. 11). Minimum (trough) plasma concentrations (C_{min}) of OC achieved steady-state levels by Day 2 for 15/650 formulations and by Day 3 for the commercially-available immediate release tablet.

TABLE 24

Oxycodone Pharmacokinetic Parameters					
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
A: One tablet Day 1 (N = 20)	18.79 (5.00)	149.68 ^c (37.92)	4.00 (2.00-8.00)	0.25 (0.00-0.50)	Day 1
B: Two tablets Day 1 (N = 20)	33.57 (8.41)	280.45 ^c (62.61)	5.93 (1.00-11.92)	0.00 (0.00-0.25)	Day 1
C: Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP) Day 1 (N = 20)	36.02 (10.52)	278.60 ^c (67.17)	7.50 (0.75-11.92)	0.00 (0.00-0.33)	Day 1
A: One tablet Day 5 (N = 20)	27.26 (6.33)	223.10 ^c (59.45)	3.00 (1.00-5.92)	Day 5	6.06 ^d (1.91)
B: Two tablets Day 5 (N = 20)	50.70 (10.95)	433.37 ^c (93.21)	3.00 (2.00-7.00)	Day 5	6.35 (1.89)
C: Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP) Day 5 (N = 20)	52.41 (12.40)	435.70 ^c (98.68)	2.00 (0.50-8.02)	Day 5	5.93 ^d (1.68)

^a T_{max} and t_{lag} median (minimum-maximum)^cDay 1 - $AUC_{0-12 h}$; Day 5 - $AUC_{0-12 hss}$ ^dN = 19

On Day 5 of the study, the maximum plasma OC concentration at steady-state (C_{max}^{ss}) was 27.3 ng/mL following 4.5 days of dosing with 1 tablet of 15 mg OC/650 mg APAP administered every 12 hours. C_{max}^{ss} following 2 tablets of 15 mg OC/650 mg APAP administered every 12 hours or the commercially-available immediate release tablet administered Q6 hours for 4.5 days were 50.7 ng/mL and 52.4 ng/mL,

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respectively. Median T_{max}^{ss} was observed at 3 hours following 1 tablet or 2 tablets of 15/650 and at 2 hours following the first daily dose of the commercially-available immediate release tablet.

PK parameters for APAP are presented in Table 25. Acetaminophen was rapidly absorbed following a single dose of 1 or 2 tablets of 15/650 and in a similar fashion to the commercially-available immediate release tablet (see FIG. 12). There was no lag in plasma concentrations following any of the three dosing regimens. Peak APAP plasma concentrations were observed at 1 hour after administration of 1 or 2 tablets of 15/650 and at 0.9 hours after the first dose of the commercially-available immediate release tablet on Day 1. After a single administration of 15/650, C_{max} for APAP was

TABLE 25

Acetaminophen Pharmacokinetic Parameters					
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
A: One tablet Day 1 (N = 20)	3942 (1168)	22928 ^c (7331)	1.00 (0.50-5.93)	0.00 (0.00-0.28)	Day 1
B: Two tablets Day 1 (N = 20)	7536 (2205)	44254 ^c (13885)	1.00 (0.28-4.00)	0.00 (0.00-0.25)	Day 1

proportional with respect to the amount of APAP in 1 or 2 tablets of 15/650 (i.e., 1 tablet—3942 ng/mL; 2 tablets—7536 ng/mL). Minimum (trough) concentrations (C_{min}) of APAP achieved steady-state levels by Day 2 for 1 tablet of 15/650, by Day 4 for 2 tablets of 15/650 and by the second dose on Day 1 for the commercially-available immediate release tablet.

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TABLE 25-continued

Acetaminophen Pharmacokinetic Parameters					
Dosage	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	T_{max}^a (hr)	T_{lag}^a (hr)	$t_{1/2}$ (hr)
C: Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP Day 1 (N = 20))	6757 (1949)	43634 ^g (12357)	0.90 (0.32-11.92)	0.00 (0.00-0.25)	Day 1
A: One tablet Day 5 (N = 20)	4635 (1330)	26968 ^g (9134)	1.00 (0.50-3.00)		Day 5 7.06 (2.24)
B: Two tablets Day 5 (N = 20)	8206 (2666)	50221 ^g (18415)	1.00 (0.30-4.00)		Day 5 7.46 (1.85)
C: Commercially-available immediate release tablet (7.5 mg OC/325 mg APAP Day 5 (N = 20))	7433 (1979)	50678 ^g (15565)	1.50 (0.25-8.02)		Day 5 6.79 ^h (2.47)

^a T_{max} and t_{lag} median (minimum-maximum)^gDay 1 - $AUC_{0-12 h}$; Day 5 - $AUC_{0-12 h}^{ss}$ ^hN = 17

On Day 5 of the study, median T_{max}^{ss} for APAP was observed at 1 hour following 1 or 2 tablets of 15/650 and at 1.5 hours following the first daily dose of the commercially-available immediate release tablet on Day 5. Maximum plasma APAP concentration at steady-state (C_{max}^{ss}) was 4635 ng/mL following 4.5 days of dosing with 1 tablet of 15/650 every 12 hours (Table 25). C_{max}^{ss} following 2 tablets of 15/650 administered every 12 hours and for the commercially-available immediate release tablet administered Q6 hours for 4.5 days were 8206 and 7433 ng/mL, respectively.

Example 6

Clinical Pharmacokinetic Analysis of
Controlled-Release 15 mg Oxycodone/650 mg
Acetaminophen Bilayer Tablets Under Fed and
Fasted Conditions

Two open-label, randomized, two-period crossover studies were conducted to evaluate the effect of food on the pharma-

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cokinetics, bioavailability and safety of the 15 mg oxycodone/650 mg APAP composition (see selected example from Chart No. 2) using a 1 tablet or 2 tablet dosing configuration in normal, healthy subjects. Studies were conducted in 48 subjects under fed (FDA high fat breakfast) or fasted conditions.

Tables 26 and 27 present the pharmacokinetic data for oxycodone (OC) and APAP, respectively. FIGS. 13 and 14 present the plasma concentration of OC following administration of one tablet and two tablets, respectively, under fed (Treatment A) or fasted (Treatment B) conditions. FIGS. 15 and 16 present the plasma concentration of APAP following administration of one tablet and two tablets, respectively, under fed (Treatment A) or fasted (Treatment B) conditions.

TABLE 26

Oxycodone Pharmacokinetics (15/650)							
Dose	State (N)	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max}^a (hr)	t_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet	fed (28)	19.03 (4.20)	219.23 (55.99)	221.06 (55.88)	5.00 (1.00-12.00)	0.25 (0.00-0.50)	3.94 (0.69)
Two tablets	fed (17)	30.58 (6.57)	414.01 (104.76)	415.88 (104.86)	5.00 (0.75-12.00)	0.25 (0.00-0.27)	4.42 (0.97)
One tablet	fasted (28)	18.31 (4.67)	196.51 (53.04)	198.33 (52.82)	3.50 (0.50-10.00)	0.00 (0.00-0.25)	4.25 (0.59)
Two tablets	fasted (17)	33.69 (7.45)	390.33 (145.27)	392.15 (145.81)	5.00 (2.00-5.20)	0.00 (0.00-0.25)	4.80 (1.07)

^a T_{max} and t_{lag} median (minimum-maximum)

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Plasma concentrations (Table 26; FIGS. 13 and 14) of OC rose rapidly with the median T_{max} observed at about 4 to 5 hr under both fed and fasted conditions for both the 1- and 2-tablet dose configurations. OC plasma levels were biphasic—with a first peak at about 3 hours and a second peak at about 5 hours. The C_{max} values (at 5 hours) for OC under fed (1 and 2 tablets, 19.0 and 30.6 ng/mL) conditions were equivalent to those observed under fasted (1 and 2 tablets, 18.3 and 33.7 ng/mL) conditions for both the 1 tablet and 2 tablet dosing configurations.

TABLE 27

Acetaminophen Pharmacokinetics (15/650)							
Dose	State (N)	C_{max} (ng/mL)	AUC_{0-t} (ng · hr/mL)	AUC_{0-inf} (ng · hr/mL)	T_{max}^a (hr)	t_{lag}^a (hr)	$t_{1/2}$ (hr)
One tablet	fed (28)	4374 (1286)	31480 (9316)	32552 (9489)	1.00 (0.50, 5.00)	0.00 (0.00-0.50)	4.65 (1.26)
Two tablets	fed (17)	6341 (1698)	62904 (19294)	68839 ^b (19826)	2.00 (0.75-6.00)	0.00 (0.00-0.25)	7.02 ^b (1.77)
One tablet	fasted (28)	5511 (2095)	31876 (103339)	33860 (10731)	0.75 (0.25, 5.00)	0.00 (0.00-0.25)	5.19 ^c (1.50)
Two tablets	fasted (17)	10428 (3529)	61164 (16552)	65281 (15711)	0.75 (0.25-5.00)	0.00 (0.00-0.00)	5.6 (1.49)

^a T_{max} and t_{lag} median (minimum-maximum)^bN = 12^cN = 27^dN = 13

Plasma concentrations (Table 27; FIGS. 15 and 16) of APAP rose rapidly following 1 tablet dosed under fed and fasted conditions with similar T_{max} values (1.0 hour and 0.8 hour). T_{max} was observed sooner following 2 tablets given under fasted conditions (0.8 hour) than under fed conditions (2 hours). Plasma concentrations of APAP were lower under fed conditions than under fasted conditions with fed C_{max} values of 4374 ng/mL (1 tablet) and 6341 ng/mL (2 tablets) and fasted C_{max} values of 5511 ng/mL (1 tablet) and 10,428 ng/mL (2 tablets). Nevertheless, the peak concentrations demonstrate that there was only a slight, minimal food effect on the absorption of APAP, which is consistent with that observed for other oxycodone and acetaminophen products. Thus, there is no meaningful food effect seen with this composition, and as such, the composition can be administered without regard to food.

Example 7

Abuse Potential of Controlled-Release Formulations

It has long been theorized that the desirability of a drug of abuse is related to the speed with which it reaches maximum concentration in the plasma of the user. Basic science and clinical observation suggest that a shortened time to maximum plasma concentration (t_{max}) and a heightened maximum plasma concentration (C_{max}) would increase the euphoric effects conferred by a drug. The abuse quotient (AQ) is a relatively new concept that attempts to predict the abuse potential of drugs. The AQ refers to the two PK parameters expressed as a ratio: $AQ = C_{max}/t_{max}$. The abuse potential of a drug increases as the value of the AQ increases, either by heightening C_{max} or shortening t_{max} .

Table 28 presents the AQs for various extended release formulations disclosed herein (see, e.g., selected examples from Chart Nos. 1 and 2) and several commercially available formulations.

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TABLE 28

Abuse Quotient			
Formulation	C_{max} (ng/mL)	t_{max} (hr)	AQ
15/500—Fast	18.8	4.95	3.80
15/500—Medium	18.27	5.31	3.44
15/500—Slow	17.4	5.66	3.07
15/650—1 tablet	17.68	3.90	4.53

TABLE 28-continued

Abuse Quotient			
Formulation	C_{max} (ng/mL)	t_{max} (hr)	AQ
15/650—2 tablets	14.59*	5.03	2.90
7.5/325—1 tablet	16.82	3.71	4.53
7.5/325—2 tablets	16.39	3.17	5.17
Percocet	22.43	2.16	10.38
Oxycontin	17.35	3.54	4.90
OxyER	19.61	4.11	4.77

*dose normalized to 15 mg

Example 8

Ethanol Release Testing at a 150 rpm Paddle Speed

To assess the potential for dose dumping, the in vitro dissolution of oxycodone and APAP from 7.5 mg OC/325 mg APAP tablets was tested in 0.1 N HCl containing 0%, 5%, 20%, or 40% v/v ethanol. The ER layer of the 7.5/325 tablets contained 5.625 mg of OC, 162.5 mg of APAP, and 45% (w/w) POLYOX® 1105, and the IR layer contained 1.875 mg of OC and 162.5 mg of APAP. (See selected example from Chart No. 1.) For each profile, twelve tablets were weighed, placed in a sinker, and dropped into an equilibrated USP Type II apparatus (paddles) that contained 900 mL of (helium sparged) 0.1 N HCl (containing either 0%, 5%, 20%, or 40% ethanol) heated to ~37° C. The mixture was stirred at ~150 rpm and the temperature was maintained at ~37° C. for 120 minutes. The bath vessel was covered with a low evaporation vessel cover. Samples were removed at 15, 30, 45, 60, 75, 90, 105, and 120 minutes. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

Tables 29, 30, 31, and 32 present the percent release of OC and APAP in the presence of 0%, 5%, 20%, and 40% ethanol, respectively. FIG. 17 presents dissolution profiles for OC and

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FIG. 18 presents dissolution profiles for APAP in the presence of 0%, 5%, 20%, and 40% ethanol. These data reveal that, for both OC and APAP, the dissolution in 5%, 20%, or 40% ethanol was either comparable or slower than the dissolution in 0% ethanol, indicating no dose dumping for this formula- 5

TABLE 29

Percent Release in 0% Ethanol								
OC					APAP			
Time (Min)	Mean	RSD	Mini-mum	Maximum	Mean	RSD	Mini-mum	Maximum
15	32.0	2.7	31.1	33.4	52.9	2.7	50.6	56.0
30	37.6	2.4	36.5	39.2	55.6	2.5	53.5	58.6
45	42.3	2.6	40.9	44.4	58.1	2.5	56.0	61.1
60	46.5	2.5	45.0	48.7	60.5	2.4	58.4	63.5
75	50.4	2.5	48.7	52.5	62.9	2.4	60.8	65.9
90	54.1	2.4	52.1	56.2	65.0	2.3	62.9	68.0
105	57.7	2.1	55.6	59.8	67.1	2.3	65.0	70.1
120	61.1	2.2	58.9	63.5	69.1	2.2	66.9	72.1

TABLE 30

Percent Release in 5% Ethanol								
OC					APAP			
Time (Min)	Mean	RSD	Mini-mum	Maximum	Mean	RSD	Mini-mum	Maximum
15	31.2	2.4	30.2	32.4	52.1	1.5	50.5	53.5
30	36.9	3.2	35.1	39.0	54.9	1.6	53.4	56.4
45	41.5	3.3	39.1	44.0	57.2	1.5	55.7	58.7
60	45.5	3.5	43.4	48.2	59.4	1.5	57.9	60.9
75	49.4	2.6	47.9	52.5	61.5	1.5	60.0	63.0
90	52.9	3.5	50.7	56.1	63.4	1.5	61.9	65.0
105	56.2	1.8	54.0	57.8	65.4	1.5	63.8	66.9
120	59.3	2.8	56.7	61.7	67.2	1.5	65.6	68.7

TABLE 31

Percent Release in 20% Ethanol								
OC					APAP			
Time (Min)	Mean	RSD	Mini-mum	Maximum	Mean	RSD	Mini-mum	Maximum
15	28.5	4.1	26.5	30.3	51.3	2.9	48.2	53.1
30	33.6	3.3	32.3	35.7	54.1	2.3	51.3	55.7
45	38.3	2.8	35.7	39.9	56.3	2.2	53.7	58.0
60	41.8	3.6	38.1	44.1	58.3	2.1	55.6	59.9
75	45.6	3.0	43.4	48.8	60.2	2.0	57.7	61.8
90	48.7	3.3	46.1	52.0	62.0	2.0	59.4	63.6
105	51.4	3.0	49.1	53.7	63.7	1.9	61.1	65.2
120	54.3	2.7	51.3	56.7	65.4	1.9	62.9	66.8

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TABLE 32

Percent Release in 40% Ethanol								
OC					APAP			
Time (Min)	Mean	RSD	Mini-mum	Maximum	Mean	RSD	Mini-mum	Maximum
15	10.3	16.3	7.8	13.7	20.7	16.3	15.8	25.9
30	20.7	8.6	16.5	23.0	37.1	7.7	31.4	41.4
45	28.6	10.4	24.4	33.4	44.4	2.6	42.2	45.8
60	31.3	5.9	29.2	35.0	47.0	1.4	45.9	48.0
75	34.5	6.5	30.3	38.1	49.0	1.4	47.7	49.8
90	36.8	7.0	33.9	41.2	50.5	1.5	49.2	51.6
105	38.5	6.8	35.3	44.0	51.9	1.7	50.4	53.1
120	40.7	4.5	38.0	43.5	53.2	1.4	51.5	54.1

Example 9

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of Oxycodone/Acetaminophen Administered Under Fed and Fasted Conditions

An open-label, randomized, three-period crossover study was conducted to evaluate the pharmacokinetics (PK), bio-availability, and safety of two tablets of a multi-layer extended-release formulation (each tablet comprising 7.5 mg oxycodone hydrochloride/325 mg acetaminophen), adminis- 25 tered as a single dose in normal, healthy subjects under fed (high-fat or low-fat meal) and fasted conditions (i.e., 10 hr fast).

This single center, open-label, randomized, 3-period, 6-se-quence crossover study in normal, healthy subjects was designed to evaluate the effect of a high-fat and low-fat meal on the PK, bioavailability, and safety of a multilayer ER tablet formulation of 7.5 mg OC/325 mg APAP (see selected 35 example from Chart No. 1). The formulation was orally administered as 2 tablets (15 mg OC/650 mg APAP total dose) under 2 types of fed (high-fat and low-fat) and fasted conditions. Forty-eight subjects were enrolled and 31 sub-jects completed the study. Only subjects that completed all 3 study periods have been included in the PK evaluation.

Following a 10 hour overnight fast, subjects randomized to Treatment A consumed an entire standardized FDA high-fat breakfast (approximately 1,000±100 calories and approxi- 45 mately 50% from fat); those receiving Treatment B consumed an entire low-fat breakfast (approximately 800±80 calories and approximately 25% to 30% from fat). Breakfasts were consumed within 30 minutes prior to Hour 0 study drug administration. Subjects who could not consume the entire breakfast in the allotted time were dropped from the study. 55 Subjects randomized to Treatment C were administered study drug under fasted conditions following an overnight fast of at least 10 hours. No food was allowed for the first 4 hours postdose. Blood samples were collected pre-dose (up to 60 minutes prior to dose), and at 15 min, 30 min, 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 18, 20, 24, 36 and 48 hours 60 post-dose, and the resulting plasma samples were analyzed for OC and APAP using a validated liquid chromatography-tandem mass spectrometry assay with a linear range of 0.100 to 100 ng/mL for OC and 100 to 50,000 ng/mL for APAP. Pharmacokinetic parameters, as detailed above in Example 2, were determined.

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Tables 33 and 34 presents PK parameters for OC under the three treatment conditions, and FIG. 19 presents plasma OC concentration-time profiles for the treatments. Mean plasma concentration profiles of OC revealed that OC was rapidly absorbed under both fed (high and low fat meal) and fasted conditions. There was a slight lag (median 0.25 hours) when the formulation was administered after a meal (high and low fat). The median of the time of observed maximum plasma concentrations (T_{max}) were 4 hours and 3 hours after administration under low fat and fasted conditions, respectively. Median T_{max} for OC under high fat conditions was significantly delayed, as compared to fasted conditions (5 hr vs. 3 hr; $P < 0.05$). Average maximum plasma OC concentrations (C_{max}) were 19.94 ng/mL after a low fat breakfast, 17.90 ng/mL after a high fat breakfast, and 15.91 ng/mL under fasted conditions.

TABLE 33

Oxycodone Pharmacokinetic Estimates (2 tablets of 7.5/325)			
	Treatment A	Treatment B	Treatment C
	High Fat	Low Fat	Fasted
Parameter	Mean (SD) (N = 31)	Mean (SD) (N = 31)	Mean (SD) (N = 31)
AUC_{0-t} (ng · h/mL)	219.41 (54.07)	219.49 (57.29)	190.70 (50.03)
AUC_{0-inf} (ng · h/mL)	221.00 (54.14)	221.38 (56.95)	192.63 (49.69)
C_{max} (ng/mL)	17.90 (4.25)	19.94 (4.66)	15.91 (3.43)
T_{max} (h) ^a	5.00 (1.00-12.00)	4.00 (1.00-5.00)	3.00 (0.75-8.00)
K_{el} (1/h)	0.1682 (0.0298)	0.1693 (0.0321)	0.1502 (0.0269)
t_{lag} (h) ^a	0.25 (0.00-1.00)	0.25 (0.00-0.75)	0.00 (0.00-0.25)
$t_{1/2}$ (h)	4.26 (0.83)	4.26 (0.91)	4.76 (0.87)

^aMedian (minimum-maximum).

A comparison of C_{max} showed that OC concentrations were 12% and 25% higher when the formulation was given under high fat (Treatment A) and low fat (Treatment B) conditions, compared to fasted conditions (Treatment C; see Table 33). The C_{max} for Treatment A was bioequivalent to both Treatments B (84%-96%) and C (105%-120%) as the 90% CIs for the geometric ratios were contained within 80% to 125% (see Table 34). The C_{max} observed for Treatment B was not bioequivalent to Treatment C (117%-134%). AUCs were approximately 15% higher when the formulation was administered under fed conditions (high and low fat), as compared to fasted conditions (Table 33). AUC for both Treatments A and B (high fat and low fat) were bioequivalent to Treatment C (fasted; 111%-121% and 111%-120% for AUC_{0-t} and 111%-120% and 110%-120% for AUC_{0-inf}) (Table 34). The apparent plasma terminal elimination half-life ($t_{1/2}$) for OC was similar when the formulation was administered under fed (4 hours) and fasted conditions (5 hours).

TABLE 34

Oxycodone Geometric LSMEANS Ratio (%) (90% CI)			
	Treatment A/C	Treatment B/C	Treatment A/B
Parameter	Fed (High Fat)/Fasted	Fed (Low Fat)/Fasted	Fed (High Fat)/Fed (Low Fat)
AUC_{0-t} (ng · h/mL) ^a	115.41 (110.63, 120.41)	115.09 (110.38, 120.01)	100.28 (96.18, 104.55)

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TABLE 34-continued

Oxycodone Geometric LSMEANS Ratio (%) (90% CI)			
	Treatment A/C	Treatment B/C	Treatment A/B
Parameter	Fed (High Fat)/Fasted	Fed (Low Fat)/Fasted	Fed (High Fat)/Fed (Low Fat)
AUC_{0-t} (ng · h/mL) ^a	115.85 (111.00, 120.90)	115.30 (110.54, 120.27)	100.47 (96.34, 104.79)
C_{max} (ng/mL) ^a	112.11 (104.61, 120.16)	125.16 (116.88, 134.03)	89.57 (83.67, 95.90)

^aN = 31.

PK parameters for APAP are presented in Tables 35 and 36 and the plasma APAP concentration-time profiles are presented in FIG. 20. APAP was rapidly absorbed following administration under fed (high and low fat meals) and fasted conditions. There was a slight lag when the formulation was administered after a low fat breakfast (median lag time [t_{lag}] 0.25 hours). There was no lag in the absorption of APAP when administered following a high fast breakfast or after fasting. The time to C_{max} was significantly ($P < 0.05$) longer when administered after a meal (high and low fat; median T_{max} = 2 hours) than when administered under fasted conditions (median T_{max} = 0.5 hour). Average C_{max} values for APAP were lower after a high (3,775 ng/mL) and low fat (3,863 ng/mL) meal than when administered under fasted conditions (5,175 ng/mL). Geometric mean ratios for C_{max} following Treatments A and B were 24% to 23% lower than for Treatment C (Table 36). The 90% CIs for C_{max} following Treatment A (70%-82%) and Treatment B (72%-83%) with reference to fasted state were outside the bioequivalent range of 80%-125%. The AUCs for APAP were almost identical when the formulation was administered under high fat, low fat, or fasting conditions. (Comparison of geometric mean ratios of AUC_{0-t} and AUC_{0-inf} for Treatments A (90% CI 97%-103% and 96%-102%) and B (90% CI 96%-101% and 94% to 100%) with those for Treatment C showed that treatments were bioequivalent. The $t_{1/2}$ for APAP after the formulation was administered after a high or low fat meal (5 hours) was slightly shorter than when administered under fasted conditions (7 hours).

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TABLE 35

APAP Pharmacokinetic Estimates (2 tablets of 7.5/325)			
Parameter	Treatment A Fed (High Fat) Mean (SD) (N = 31)	Treatment B Fed (Low Fat) Mean (SD) (N = 31)	Treatment C Fasted Mean (SD) (N = 31)
AUC _{0-t} (ng · h/mL)	29617.96 (7765.99)	29346.82 (7869.75)	29763.19 (7592.89)
AUC _{0-∞} (ng · h/mL)	31457.06 (7973.16) ^a	30550.48 (8051.47)	31807.70 (7923.30) ^a
C _{max} (ng/mL)	3774.52 (949.84)	3862.90 (978.08)	5175.48 (1731.31)
T _{max} (h) ^b	2.00 (0.50-5.00)	2.00 (0.50-5.00)	0.53 (0.23-5.00)
K _{el} (1/h)	0.1564 (0.0363) ^a	0.1593 (0.0408)	0.1146 (0.0360) ^a
t _{lag} (h) ^b	0.00 (0.00-1.00)	0.25 (0.00-0.50)	0.00 (0.00-0.25)
t _{1/2} (h)	4.66 (1.08) ^a	4.71 (1.60)	6.63 (1.99) ^a

^aN = 29^bMedian (minimum-maximum).

TABLE 36

APAP Geometric LSMEANS Ratio (%) (90% CI)			
Parameter	Treatment A/C Fed (High Fat)/Fasted	Treatment B/C Fed (Low Fat)/Fasted	Treatment A/B Fed (High Fat)/ Fed (Low Fat)
AUC _{0-∞} (ng · h/mL) ^a	98.60 (95.75, 101.54)	96.56 (93.80, 99.39)	102.12 (99.20, 105.11)
AUC _{0-t} (ng · h/mL) ^b	99.88 (97.31, 102.52)	98.79 (96.27, 101.37)	101.10 (98.54, 103.74)
C _{max} (ng/mL) ^b	76.00 (70.49, 81.94)	77.18 (71.65, 83.13)	98.48 (91.45, 106.05)

^aN = 27^bN = 31.

In summary, total exposure (AUC) for OC was slightly increased (by about 15%) when the formulation was administered with food (after high- or low-fat meal); however, AUCs for OC were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted and high fat vs. low fat). Peak exposure (C_{max}) for OC was 12% and 25% higher under high fat and low-fat conditions, respectively, compared to fasted conditions. The C_{max} for OC after a high-fat meal was bioequivalent to fasted conditions, as well as to low fat conditions, whereas the C_{max} under low fat conditions was not equivalent to those under fasted conditions. The AUCs for APAP were equivalent between all treatments (high fat vs. fasted, low fat vs. fasted, and high fat vs. low fat). The peak exposure (C_{max}) for APAP was decreased by about 24% in fed (high- and low-fat) states as compared to the fasted state.

Example 10

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Oxycodone/325 mg Acetaminophen—Single Dose

An open-label, randomized, 3-period crossover study was performed to evaluate the single dose pharmacokinetic (PK)

parameters, bioavailability, and safety of an extended-release formulation containing 7.5 mg OC/325 mg APAP (see selected example from Chart No. 1) in healthy subjects under fasted conditions. The PK and bioavailability of the extended-release formulation administered as 1 or 2 tablets were compared to the commercially-available immediate release tablet (immediate release 7.5 mg OC/325 mg APAP) administered as 1 or 2 tablets every 6 hours for 2 doses. This study was conducted in 48 male and female subjects, with equal gender distribution.

Pharmacokinetic parameter estimates for OC are presented in Table 37, and OC plasma concentration-time profiles are presented in FIG. 21. There was no lag in absorption of OC for the 1 and 2 tablet dosing configurations of the extended release formulation and the commercially-available immediate release tablet under fasted conditions. Plasma concentrations of OC rose rapidly after administration of the extended release formulation in a similar fashion to the commercially-available immediate release tablet, and peak plasma levels of OC were observed (T_{max}) at 4 and 3 hours for the 1 or 2 tablet dosing configuration of the extended release formulation compared with 7 hours after the initial dose of 1 tablet of the commercially-available immediate release tablet (1 hour after the second dose) and 0.75 hours after the initial dose of 2 tablets of the commercially-available immediate release tablet. Mean plasma concentrations of OC from the extended release formulation were detectable through 36 hours in most subjects following all treatments and t_{1/2} was about 4 to 5 hours across all treatments. The extent of exposure (AUC_{0- t} and AUC_{0- ∞}) for the 2 tablet dosing configuration of the extended release formulation increased proportionally with dose compared with the 1-tablet dosing configuration of the extended release formulation.

TABLE 37

Oxycodone Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
AUC _{0-t} (ng · h/mL)	87.43 (24.59)	185.98 (47.64)	191.15 (53.43)	401.23 (110.56)
AUC _{0-∞} (ng · h/mL)	89.85 (24.73) ^b	187.71 (47.58)	193.10 (53.22)	403.04 (110.45)

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TABLE 37-continued

Oxycodone Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
C_{max} (ng/mL)	8.41 (2.06)	16.39 (4.31)	20.82 (5.98)	41.24 (12.12)
T_{max} (h) ^a	4.00 (0.75-5.92)	3.00 (0.75-6.50)	7.38 (0.50-10.00)	0.75 (0.50-12.00)
t_{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.52)	0.00 (0.00-0.25)	0.00 (0.00-0.25)
$t_{1/2}$ (h)	4.50 (0.78) ^b	4.87 (0.93)	4.08 (0.89)	4.34 (1.02)
K_{el} (h ⁻¹)	0.1590 (0.0307) ^b	0.1473 (0.0274)	0.1770 (0.0352)	0.1688 (0.0415)

^aMedian (minimum-maximum).^bN = 32

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No dose-dumping was observed in any subject receiving the ER formulation. The interindividual variability (CV %) for C_{max} of OC after administration of 1 or 2 tablets of the ER formulation was comparable to 1 tablet of the commercially-available immediate release tablet and less than 29% for all 3

detectable through 36 hours following all treatments and the mean $t_{1/2}$ was approximately 4 to 7 hours across treatment groups. The extent of exposure (AUC) to APAP following dosing with 1 and 2 tablets of the extended release formulation increased proportionally with dose.

TABLE 38

APAP Pharmacokinetic Estimates (7.5/325)				
Parameter	Treatment A ER Formulation (1 tablet) Mean (SD) (N = 33)	Treatment B ER Formulation (2 tablets) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 tablet twice) Mean (SD) (N = 33)	Treatment D Commercially- available immediate release tablet (2 tablets twice) Mean (SD) (N = 27)
AUC_{0-t} (ng · h/mL)	15871 (4841)	32665 (10894)	33040 (9589)	69837 (22945)
AUC_{0-inf} (ng · h/mL)	16995 (5073)	34836 (11067) ^b	34236 (10126) ^b	71949 (24234) ^c
C_{max} (ng/mL)	2632 (918)	5230 (2086)	4878 (1545)	10741 (4123)
T_{max} (h) ^a	0.75 (0.25-2.02)	0.75 (0.25-4.00)	0.50 (0.25-9.00)	0.50 (0.25-12.00)
t_{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.25)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
$t_{1/2}$ (h)	5.33 (1.53)	6.88 (2.15) ^b	4.41 (1.16) ^b	5.76 (1.47) ^c
K_{el} (h ⁻¹)	0.1421 (0.0479)	0.1103 (0.0337) ^b	0.1669 (0.0411) ^b	0.1291 (0.0368) ^c

^aMedian (minimum-maximum).^bN = 32^cN = 25

treatments. Similarly the interindividual variability (CV %) for AUC of OC was 28% or less for 1 and 2 tablets of the ER formulation and 1 tablet of the commercially-available immediate release tablet.

Table 38 presents APAP PK parameter estimates and FIG. 22 presents APAP plasma concentration-time profiles. The appearance of plasma concentrations of APAP for all dose configurations of the extended release formulation and the commercially-available immediate release tablet showed no lag. Plasma concentrations of APAP rose rapidly after administration of the extended release formulation, similar to that observed with the commercially-available immediate release tablet. Peak plasma levels of APAP following administration of the 1 tablet and 2 tablet dosing configurations of the extended release formulation were observed (median T_{max}) at 0.75 hours after dosing compared with 0.5 hours after the first dose of the commercially-available immediate release tablet (1 and 2 tablets). Mean plasma concentrations of APAP were

No dose-dumping was observed in any subject receiving the ER formulation. The interindividual variability (CV %) for C_{max} of APAP was slightly more after administration of 1 and 2 tablets of the ER formulation (35% and 40%, respectively) than for 1 tablet of the commercially-available immediate release tablet (32%). The interindividual variability (CV %) for AUC of APAP was less than 33% for all 3 treatments.

Both OC and APAP were rapidly absorbed under all conditions with no lag in plasma concentrations. Both OC and APAP levels were sufficiently high within 1 hour after administration of the extended release formulation. Peak exposure to OC was 18% to 21% lower for the ER formulation than for the commercially-available immediate release tablet (1 tablet Q6h). OC levels were sustained over the proposed 12 h dosing interval. By 12 hours after dosing with the extended release formulation, APAP plasma levels were less than 20% of C_{max} . Total exposure to both OC and APAP from the extended release formulation was equivalent to that of 1 tablet of the commercially-available immediate release tablet.

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To further analyze the absorption of OC and APAP from the ER formulation, the plasma concentrations of OC and APAP following administration of 1 tablet of the ER formulation, 2 tablets of the ER formulation, and the commercially-available immediate release tablet were deconvolved using Win-Nonlin 5.2 (Pharsight). Deconvolution evaluates in vivo drug release and delivery based on data for a known drug input. Depending upon the type of reference input information available, the drug transport evaluated will be either a simple in vivo drug release (e.g., gastro-intestinal release) or a composite form, typically consisting of an in vivo release followed by a drug delivery to the general systemic circulation. It can estimate the cumulative amount and fraction absorbed over time for the subjects, given PK profile data and dose. For a pure immediate release (IR) or an extended release (ER) formulation the cumulative absorption plot shows a monoexponential curve whereas for a bilayer formulation (IR+ER) a biexponential (rapid phase followed by slower phase) absorption curve will be observed. FIG. 23 and FIG. 24 present the deconvolution plots for OC and APAP, respectively. For each, there is an early rapid phase of absorption that is followed by a later slower phase of absorption from the ER formulation.

Example 11

Clinical Pharmacokinetic Analysis of an Extended Release Formulation of 7.5 mg Oxycodone/325 mg Acetaminophen—Multiple Doses

An open-label, randomized, 3-period crossover study was performed to evaluate the steady-state PK, bioavailability, and safety of the extended release formulation containing 7.5 mg OC/325 mg APAP in healthy subjects (see selected example from Chart No. 1). The PK and bioavailability of the ER formulation administered as 1 or 2 tablets every 12 hours for 4.5 days (9 doses) was compared to the commercially-available immediate release tablet (immediate release 7.5 mg OC/325 mg APAP) administered as 1 tablet every 6 hours for 4.5 days (18 doses) under fasted conditions (10 hours for the first dose on Days 1 and 5; at least 1 hour for all other doses). This study was conducted in 48 male and female subjects, with equal gender distribution.

The PK behavior of OC on Study Day 1 (see Table 39) was similar to that observed in the single dose study (see Example 10). There was no lag (median t_{lag} 0 hours) in the absorption of OC following administration of the ER formulation (1 or 2 tablets) and the commercially-available immediate release tablet, and no dose-dumping was observed for any subject. Peak plasma levels were observed at 3 hours after adminis-

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tration of 1 and 2 tablets of the ER formulation and at 1 hour after the second dose of the commercially-available immediate release tablet (FIG. 25). On Day 1, interindividual variability (% CV) in the C_{max} for OC was slightly higher for 1 tablet (29%) than for 2 tablets (23%) of the ER formulation or the commercially-available immediate release tablet (up to 22%). The variability in the AUC_{0-12h} for OC was comparable between all 3 treatments (21% to 23%). Minimum (trough) plasma concentrations (C_{min}) of OC achieved steady-state levels by Day 4 for 1 tablet of the ER formulation and the commercially-available immediate release tablet and by Day 3 for 2 tablets of the ER formulation. Trough levels of OC on Days 2 through 5 for 2 tablets of the ER formulation were comparable to those observed for the commercially-available immediate release tablet.

TABLE 39

Oxycodone Pharmacokinetic Estimates - Day 1			
Parameter	Treatment A ER Formulation (1 Tablet Q12h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12h) Mean (SD) (N = 33)	Treatment C Commercially-available immediate release tablet (1 Tablet Q6h) Mean (SD) (N = 33)
AUC_{0-12h} (ng · h/mL)	66.93 (15.14)	135.89 (30.81)	141.73 (29.78)
C_{max} (ng/mL)	8.34 (2.37)	17.05 (3.97)	21.93 (4.80)
T_{max} (h) ^a	3.00 (0.75-7.00)	3.00 (0.50-5.92)	7.00 (0.50-8.00)
t_{lag} (h) ^a	0.00 (0.00-0.50)	0.00 (0.00-0.32)	0.00 (0.00-0.25)

^aMedian (minimum-maximum).

On Day 5 (see Table 40), steady state was achieved and the median T_{max}^{ss} was observed at 2 hours following 1 tablet or 2 tablets of the ER formulation and at 30 min following the second daily dose of the commercially-available immediate release tablet. Maximum observed plasma concentrations at steady-state (C_{max}^{ss}) for OC for the 1 and 2 tablet dosing configurations of the ER formulation were not equivalent to the commercially-available immediate release tablet. On Day 5, interindividual variability (% CV) in C_{max}^{ss} and AUC_{0-12hr}^{ss} for OC was comparable between all 3 treatments (up to 29%). The degree of fluctuation (DFL) in and the swing of plasma concentrations for the ER formulation over the last 12 hour dosing interval on Day 5 were 15% to 22% less than that observed for the commercially-available immediate release tablet.

TABLE 40

Oxycodone Pharmacokinetic Estimates - Day 5			
Parameter	Treatment A ER Formulation (1 Tablet Q12h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12h) Mean (SD) (N = 33)	Treatment C Commercially-available immediate release tablet (1 Tablet Q6h) Mean (SD) (N = 33)
AUC_{0-12h}^{ss} (ng · h/mL)	102.36 (29.30)	208.59 (59.28)	208.93 (57.30)
C_{av}^{ss} (ng/mL)	8.53 (2.44)	17.38 (4.94)	17.41 (4.78)
C_{max}^{ss} (ng/mL)	12.67 (3.48)	25.67 (7.49)	30.50 (8.91)

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TABLE 40-continued

Oxycodone Pharmacokinetic Estimates - Day 5			
Parameter	Treatment A ER Formulation (1 Tablet Q12h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6h) Mean (SD) (N = 33)
C_{min}^{ss} (ng/mL)	4.06 (1.40)	8.98 (3.52)	8.78 (3.17)
DFL (%)	101.72 (14.14)	97.17 (18.80)	126.83 (27.93)
Swing	2.23 (0.64)	2.03 (0.70)	2.67 (0.92)
T_{max}^{ss} (h) ^a	2.00 (0.50-10.00)	2.00 (0.50-7.00)	6.50 (0.50-8.02)
$t_{1/2}$ (h) ^c	5.46 (1.24)	6.11 (1.46)	5.47 (1.70) ^b
K_{el} (1/h) ^c	0.1326 (0.0269)	0.1199 (0.0291)	0.1387 (0.0418) ^b

^aMedian (minimum-maximum).^bN = 32^cDays 5 to 7.

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The PK behavior of APAP on Study Day 1 (see Table 41) was similar to that observed in the single dose study (see Example 10). Acetaminophen was rapidly absorbed following a single dose of 1 or 2 tablets of the ER formulation and in a similar fashion to the commercially-available immediate release tablet (FIG. 26). There was no lag in plasma concentrations following any of the 3 dosing regimens (median t_{lag} 0 hours), and no dose-dumping was observed for any subject. Peak APAP plasma concentrations were observed 30 to 45 minutes after administration of 1 or 2 tablets of the ER formulation and at 30 minutes after the first dose of the commercially-available immediate release tablet on Day 1. The C_{max} for APAP occurred following the first 325 mg dose of the

commercially-available immediate release tablet, rather than after the second dose. Dose proportionality for C_{max} and AUC_{0-12h} was observed over the range of 325 mg to 650 mg APAP after a single administration of 1 or 2 tablets of the ER formulation. The C_{min} of APAP achieved steady-state levels by Day 4 for 1 tablet and by Day 2 for 2 tablets of the ER formulation and for the commercially-available immediate release tablet. Trough levels of APAP on Days 2 through 5 for 2 tablets of the ER formulation were comparable to those observed for the commercially-available immediate release tablet. On Day 1, interindividual variability (% CV) in C_{max} and AUC_{0-12h} for APAP was comparable between all 3 treatments (31% or less).

TABLE 41

APAP Pharmacokinetic Estimates - Day 1			
Parameter	Treatment A ER Formulation (1 Tablet Q12h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6h) Mean (SD) (N = 33)
AUC_{0-12h} (ng · h/mL)	12192 (3331)	24141 (6436)	24884 (6656)
C_{max} (ng/mL)	2631 (815)	5245 (1473)	5146 (1553)
T_{max} (h) ^a	0.55 (0.25-3.00)	0.75 (0.25-2.00)	0.50 (0.25-8.00)
t_{lag} (h) ^a	0.00 (0.00-0.25)	0.00 (0.00-0.25)	0.00 (0.00-0.00)

^aMedian (minimum-maximum).

On Day 5 of the study, median T_{max}^{ss} for APAP was observed at 30 minutes following 1 or 2 tablets of the ER formulation and at 30 minutes following the first daily dose of the commercially-available immediate release tablet (see Table 42). Acetaminophen concentrations following administration of 325 mg or 650 mg APAP (1 or 2 tablets) Q12h were proportional to dose. The DFL in and swing of plasma APAP levels for the ER formulation were equivalent to the commercially-available immediate release tablet. On Day 5, interindividual variability (% CV) in C_{max}^{ss} for APAP was slightly higher following administration of 2 tablets of the ER formulation (33%) than the % CV seen for 1 tablet of the ER formulation and the commercially-available immediate release tablet (~27%). Interindividual variability in AUC_{0-12h}^{ss} for APAP was comparable between all 3 treatments (up to 27%).

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TABLE 42

APAP Pharmacokinetic Estimates - Day 5			
Parameter	Treatment A ER Formulation (1 Tablet Q12h) Mean (SD) (N = 33)	Treatment B ER Formulation (2 Tablets Q12h) Mean (SD) (N = 33)	Treatment C Commercially- available immediate release tablet (1 Tablet Q6h) Mean (SD) (N = 33)
AUC _{0-12 h} ^{ss} (ng · h/mL)	15307 (4092)	28512 (7714)	28719 (7023)
C _{av} ^{ss} (ng/mL)	1276 (341)	2376 (643)	2393 (585)
C _{max} ^{ss} (ng/mL)	3117 (840)	5872 (1932)	5968 (1639)
C _{min} ^{ss} (ng/mL)	474.67 (163)	870.42 (336)	922.58 (321)
DFL (%)	212.08 (52.29)	218.06 (81.14)	213.79 (50.53)
Swing	5.95 (2.04)	6.63 (3.61)	5.94 (2.24)
T _{max} ^{ss} (h) ^a	0.50 (0.25-3.00)	0.50 (0.25-3.02)	0.50 (0.25-8.02)
t _{1/2} (h) ^c	5.60 (1.35) ^b	7.47 (2.89)	5.74 (2.98) ^b
K _{el} (1/h) ^c	0.1308 (0.0317) ^b	0.1026 (0.0292)	0.1416 (0.0515) ^b

^aMedian (minimum-maximum).^bN = 31^cDays 5 to 7.

Both OC and APAP were rapidly absorbed under all conditions with no lag in plasma concentrations. Both OC and APAP levels were sufficiently high within 1 hour after administration of the ER formulation as a single dose and at steady-state. OC levels were sustained over the proposed 12 h dosing interval. Plasma APAP concentrations decreased to below 1,000 ng/mL between doses of the ER formulation, thus minimizing the chances of its accumulation and the possibility of hepatotoxicity. Total exposure to both OC and APAP from the ER formulation was equivalent to that of the commercially-available immediate release tablet.

Example 12

Clinical Evaluation of the Safety and Analgesic Efficacy of an Extended Release Formulation of Oxycodone and Acetaminophen for Acute Pain

Pain relief for acute post-surgical pain requires immediate-release (IR) compounds acting within 1 hour of administration. These IR compounds, however, have a short half-life and require frequent administration; this is inconvenient to patients and leads to poor compliance. Such patients may benefit from an extended-release (ER) oral formulation of oxycodone hydrochloride (OC) and acetaminophen (APAP) that is designed to (1) provide the immediate-release of each drug to attain rapid therapeutic levels (within 1 hour of dosing) and (2) provide continuous release of each drug to maintain the plasma levels of each drug within therapeutic windows for sustained analgesia (up to 12 hours). Furthermore, combining analgesics with distinct mechanisms of action provides maximum efficacy while reducing the toxicity of each agent, as the amount of OC and APAP can remain within the lower, safer end of their therapeutic windows. This ER formulation may provide the advantages of both immediate and prolonged pain relief from two analgesic compounds, potentially offering greater convenience to patients and greater dosing compliance. Accordingly, a study may be conducted to demonstrate the efficacy of repeated doses of 15 mg OC/650 mg APAP versus placebo, and to determine the safety and tolerability of multiple oral doses of the OC/APAP formulation administered to subjects with acute postoperative, moderate to severe pain.

The study will be conducted in the following phases: 1) pre-treatment phase consisting of a) screening, b) surgery, and c) recovery/qualification periods; 2) double-blind phase consisting of a single dose period followed by a multiple-dose period which begins with the request of the 2nd dose of study medication, and; 3) a voluntary open-label extension phase.

The single dose period of the double-blind phase will evaluate the onset and duration of analgesia of a single dose of 15 mg OC/650 mg APAP (as two 7.5/325 tablets) versus placebo. The time from the initial dose of study medication to the onset of perceptible pain relief and to the onset of meaningful pain relief will be measured. The subject will provide additional pain assessments (e.g., pain intensity will be measured using the 11 point NPRS scale at regular intervals).

The multiple dose period of the double-blind phase will evaluate the analgesic effects of multiple doses of 15 mg OC/650 mg APAP versus placebo with subjects dosed regularly every 12 hours for 48 hours. The multiple dose period will begin upon administration of the second dose after the subject's request for additional pain relief. Pain relief and intensity will be among the data measured in this arm of the study.

After completion of study evaluations 48 hours after the 2nd dose of study medication, subjects will be encouraged to enter the open-label extension phase of the study. During this time they will be provided with doses of 15 mg OC/650 mg APAP to be taken Q12h until no longer needed, for up to 14 days. The open-label extension phase (starting 48 hours after the second dose) will evaluate the safety profile as determined by adverse events (AE) and evaluate subject satisfaction with analgesic effects.

Example 13

Clinical Evaluation of the Safety and Efficacy of an Extended Release Formulation of Oxycodone and Acetaminophen for Chronic Pain

An open label safety study of doses of 15 mg OC/650 mg APAP administered at 12 hour intervals for up to 35 days in a patient population having pain associated with osteoarthritis (OA) of the knee or hip or chronic low back pain (CLBP) may be conducted. The primary objective of the study is to deter-

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mine the safety and tolerability of doses of 15 mg OC/650 mg APAP for up to 35 days of use. Secondary objectives such as pain relief and changes in pain intensity will also be assessed.

Subjects enrolled in the study will be treated with 2 tablets of 7.5 mg OC/325 mg APAP every 12 hours (Q12h) for between 10 days and 35 days. Subjects will initially take 1 tablet of 7.5 mg OC/325 mg APAP under clinic supervision. Subjects will be observed for opioid tolerability symptoms. Subjects who experience opioid tolerability symptoms, or moderate to severe AEs, will be discontinued from the study. Subjects who do not experience opioid tolerability symptoms, or moderate to severe AEs, will be given a second tablet of 7.5 mg OC/325 mg APAP under clinic supervision. If subjects still do not experience opioid tolerability symptoms, or moderate to severe AEs, they will be sent home with supplies for dosing with 2 tablets of 7.5 mg OC/325 mg APAP Q12h for one week. If subjects do experience opioid tolerability symptoms, or moderate to severe AEs, they will be sent home with supplies for dosing with 1 tablet of 7.5 mg OC/325 mg APAP Q12h for one week.

Subjects that continue in the study beyond one week will continue to take 2 tablets Q12h for up to a total of 35 days, during which they will return to the clinic for subsequent assessments of safety and efficacy. After the Day 36 visit, subjects will be instructed to return to pre-study medication. Subjects whose pain subsides prior to the Day 36 visit, or who discontinue for other reasons will be instructed to return remaining study medication.

Example 14

Partial Areas Under the Curve for Oxycodone and Acetaminophen

Partial AUCs were calculated for a bilayer extended release tablet disclosed herein containing acetaminophen and oxycodone, and an immediate release acetaminophen and oxycodone tablet. Specifically, Partial AUCs were calculated for the acetaminophen and oxycodone tablets of (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10. These results are summarized in Tables 43-46.

TABLE 43

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.			
Study	AUC _{0-1.7 h} (ng · h/mL)	AUC _{1.7-48 h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment B (Ex. 10)	6029	28435	32644
Treatment C (Ex. 9)	5854	25539	29741

TABLE 44

Additional Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.					
Study	AUC _{0-12 h} (ng · h/mL)	AUC _{1-12 h} (ng · h/mL)	AUC _{12-36 h} (ng · h/mL)	AUC _{8-12 h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment B (Ex. 10)	25912	22615	7978	4401	32644
Treatment C (Ex. 9)	24102	20875	6854	3910	29741

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TABLE 45

Percent of AUC _{0-t} for Acetaminophen				
Study	AUC _{0-12 h} (dosing interval)	AUC _{1-12 h} (T _{max} to end of dosing interval)	AUC _{12-36 h} (end of dosing interval to last concentration)	AUC _{8-12 h}
Treatment B (Ex. 10)	79%	69%	24%	13%
Treatment C (Ex. 9)	81%	70%	23%	13%

TABLE 46

Mean (SD) Parameter Estimates for Partial AUCs for Oxycodone.			
Study	AUC _{0-2.8 h} (ng · h/mL)	AUC _{2.8-48 h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment B (Ex. 10)	28.75	158.49	185.93
Treatment C (Ex. 9)	27.89	164.27	190.66

The bioequivalence determinations between two tablets of a pharmaceutical composition described herein, each containing 7.5 mg oxycodone and 325 mg acetaminophen and an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen can be found in Tables 47 and 48.

TABLE 47

Bioequivalence Determination for Acetaminophen			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-1.7 h})	101.97	82.90	125.43
Ln(AUC _{1.7-48 h})	91.15	80.58	103.11
Ln(AUC _{0-t})	93.14	82.40	105.28

TABLE 48

Bioequivalence Determination for Oxycodone			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-2.8 h})	99.04	87.83	111.68
Ln(AUC _{2.8-48 h})	103.21	92.57	115.06
Ln(AUC _{0-t})	102.19	92.34	113.09

The results demonstrate that the plasma concentrations of both oxycodone and acetaminophen rose rapidly with no lag time for a pharmaceutical composition of the present inven-

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tion and an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen. See FIG. 29. Further, 30 minutes after administration of a dose of a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen), oxycodone levels were within the therapeutic range (>5 ng/mL). Thus, an analgesic effect will be seen in opioid naïve patients. In addition, a pharmaceutical composition of the present invention was able to maintain oxycodone levels above 5 ng/mL for up to 12 hours after dosing, suggesting that the analgesic effect may extend to the next dosing cycle.

Concentrations of acetaminophen resulting from a dose of a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen), decreased to less than 900 ng/mL ($>17\%$ of C_{max}) by 12 hours after administration. This decreased concentration of acetaminophen at the end of the dosing cycle allows for sufficient acetaminophen or “APAP time off” between doses.

Oxycodone and acetaminophen levels from a pharmaceutical composition of the present invention (i.e., 2 tablets of 7.5 oxycodone/325 acetaminophen) declined at a similar rate to an immediate release tablet comprising 7.5 mg oxycodone and 325 mg acetaminophen, with a terminal elimination half-life of approximately 4 to 5 hours.

Example 15

Partial Areas Under the Curve for Oxycodone and Acetaminophen Administered with Food

Partial AUCs were calculated for a bilayer extended release tablet disclosed herein containing acetaminophen and oxycodone, and an immediate release acetaminophen and oxycodone tablet. Specifically, Partial AUCs were calculated for the acetaminophen and oxycodone tablets of (1) Treatment A of Example 4, (2) Treatment A of Example 6 (one tablet), and (3) Treatment C of Example 4. These results are summarized in Tables 49-50.

TABLE 49

Mean (SD) Parameter Estimates for Partial AUCs for Acetaminophen.			
Study	AUC _{0-3.2 h} (ng · h/mL)	AUC _{3.2-48 h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment A (Ex. 4)	8042	23810	30245
Treatment A (Ex. 6) (one tablet)	9145	23319	31478

TABLE 50

Mean (SD) Parameter Estimates for Partial AUCs for Oxycodone.			
Study	AUC _{0-4.3 h} (ng · h/mL)	AUC _{4.3-48 h} (ng · h/mL)	AUC _{0-t} (ng · h/mL)
Treatment A (Ex. 4)	48.62 (15.99)	152.57 (49.86)	199.43 (59.47)
Treatment A (Ex. 6) (one tablet)	53.29 (17.12)	167.50 (51.83)	219.20 (55.99)

The bioequivalence determinations between the pharmaceutical composition described herein, containing 15 mg oxycodone and 650 mg acetaminophen and an immediate release product comprising 15 mg oxycodone and 650 mg acetaminophen can be found in Tables 51 and 52.

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TABLE 51

Bioequivalence Determination for Acetaminophen			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-3.2 h})	114.46	96.21	136.16
Ln(AUC _{3.2-48 h})	94.62	83.31	107.47
Ln(AUC _{0-t})	101.32	90.00	114.07

TABLE 52

Bioequivalence Determination for Oxycodone			
Parameter	LSM	90% CI	
	Ratio	Lower	Upper
Ln(AUC _{0-4.3 h})	109.87	94.98	127.08
Ln(AUC _{4.3-48 h})	109.75	94.48	127.48
Ln(AUC _{0-t})	110.53	97.39	125.44

Exposure to oxycodone and acetaminophen was comparable between Treatment A of Example 4 and Treatment A of Example 6 (one tablet). Thus, these results indicate that the release of oxycodone and acetaminophen is consistent across studies. Plasma concentration-time profiles are presented in FIGS. 30A and 30B.

The initial exposure to oxycodone (AUC_{0-4.3 h}) was slightly outside the bioequivalence parameters established by the FDA (upper 90% CI 127%). The initial exposure to acetaminophen (AUC_{0-3.2 h}) was outside of the FDA’s bioequivalence parameters (upper 90% CI 136%).

The extended (sustained) exposure to oxycodone AUC_(4.3-48 h) was slightly outside the FDA’s limit for bioequivalence (upper 90% CI 127%). However, the extended exposure to acetaminophen (AUC_{3.2-48 h}) and total exposure (AUC_{0-t}) for both oxycodone and acetaminophen was equivalent between studies.

Example 16

Mechanical Crushing into Powder Form

Drug abusers often tamper with extended release opioid-containing formulations by crushing the dosage form. This process generally serves several functions, including destroying the extended release properties of the dosage form and enabling the dosage form to be processed for unintended methods of administration, such as snorting or intravenous injection. Accordingly, comparative tamper resistance experiments were performed on a tablet dosage form of the pharmaceutical composition of the present invention containing 7.5 mg oxycodone HCl and 325 mg acetaminophen (see Chart 1) (the “product”) and a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the “comparator”).

The product and comparator tablets were subjected to standard mechanical crushing by the following means: a hammer, a pill crusher, a mortar and pestle, a knife, two spoons, a utility knife, a blender, a coffee mill, and a coffee grinder. The success or failure of the particle size reduction was then visually assessed. In some cases, a sieving analysis was also utilized to quantitatively measure if significant particle size reduction occurred. Generally, drug abusers desire to crush pharmaceutical formulations into a fine powder, as this form is convenient for processing the tablet into a snortable or injectable form.

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The results demonstrated that in most instances, the comparator was easily broken down into smaller pieces by each of the mechanical means listed above. Accordingly, in most instances, the comparator offered little tamper resistance as it could easily be mechanically crushed into a suitable powder. In contrast, the physical properties of the product tablet prevented the product tablet from being crushed into a fine powder. Indeed, in relation to the comparator, the product tablet was more difficult to break down using the methods listed above. Specifically, all of the mechanical methods described above were ineffective at producing a suitable powder from the product tablets except grinding in a mortar and pestle. Consequently, the product tablets offer improved protection from the mechanical crushing methods employed by drug abusers.

Example 17

Abuse Resistance Properties of Product Powders
Produced by Grinding Using a Mortar and Pestle

An in vitro dissolution test with human abuse liability ("HAL") predictions was conducted to determine the cumulative amount of drug released from intact and crushed tablets of the pharmaceutical compositions disclosed herein and a commercially-available immediate release oxycodone and acetaminophen tablet.

Comparator tablets (the "comparator") containing a total of 7.5 mg of oxycodone HCl and a total of 325 mg acetaminophen were obtained. Six comparator tablets were ground with a mortar and pestle and placed into capsules, while six tablets were used as is (i.e., kept intact, but placed into capsules). Dissolution profiles for the intact and crushed tablets were determined in a USP type II apparatus. Six intact tablets and six crushed tablets were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. ± 0.5° C. The mixture was stirred at 100 ± 4 rpm, and the temperature was maintained at 37° C. ± 0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 5 min, 10 min, 20 min, 30 min, and 60 min. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures. The release profile of oxycodone HCl from intact and crushed comparator is shown in FIG. 31.

Bilayer formulations described herein were prepared, each containing a total of 7.5 mg of oxycodone HCl, a total of 325 mg of acetaminophen, and an extended release polymer. Six product tablets (as defined in Example 16) were ground with a mortar and pestle and placed into capsules, while twelve product tablets were used as is. The same dissolution method as described for the intact and crushed comparator above was used to obtain release profiles for intact and crushed product tablets. However, six of the intact product tablets (labeled as "Intact") were sampled (5 mL) at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The release profiles of acetaminophen and oxycodone HCl from the intact and crushed product tablets are shown in FIGS. 32 and 33, respectively. In these figures, "intact" refers to the intact product tablets sampled at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. "HAL_Intact" refers to the intact product tablets sampled at the same time intervals as the crushed tablets, namely, 5 min, 10 min, 20 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr.

These results show that for release of oxycodone HCl from the comparator tablets, there is no substantial difference in the release profiles for crushed and intact tablets for abuse purposes. In each case, almost all of the oxycodone HCl was

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released in as little as ten minutes. In stark contrast, there are substantial differences in the release profiles for crushed and intact product tablets. The intact product tablets surprisingly exhibited a higher release rate of both active ingredients than the crushed product tablets in the first hour. This suggests that upon grinding the product tablets, the active ingredients in the immediate release portion are incorporated into the extended release portion, and the product tablet loses its immediate release characteristics. This feature may effectively negate a drug abuser's purpose for crushing the product tablet in the first place—to obtain an early onset of analgesia.

Predicted pharmacokinetic parameters were obtained for these in vitro release profiles for the crushed and intact products and comparator tablets by using in vitro in vivo correlation ("IVIVC") technique. These results, which are summarized in Table 53, demonstrate that the abuse quotients for the crushed and intact comparator tablets are orders of magnitude higher than the abuse quotients for the crushed and intact product tablets. This is consistent with the experimentally determined pharmacokinetic parameters from Example 10.

TABLE 53

Predicted pharmacokinetic parameters and abuse quotient for intact and crushed product and comparator tablets.

Product	C _{max} (ng/mL)	T _{max} (hr)	Abuse Quotient (ng/mL · hr)
Predicted			
Comparator (intact)	32.5	0.16	203.1
Comparator (crushed)	30.8	0.17	181.2
Product (intact)	17.5	6	2.9
Product (crushed)	20.6	4	5.2
Experimental - see Example 10			
Comparator (intact)	41.6	0.7	59.4
Product (intact)	16.4	3.2	5.1

Example 18

Preconditioning the Tablets by Crisping

Drug abusers often precondition the tablet by a process known as crisping. This procedure is intended to remove some of the tablet fillers, making the drug easier to crush and insufflate or inject. Accordingly, an experiment was performed to determine a drug abuser's ability to crisp a tablet dosage form of the pharmaceutical composition of the present invention containing 7.5 mg oxycodone HCl and 325 mg acetaminophen (see Chart 1) (the "product") as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the "comparator").

First, the product and comparator tablet were crushed into a powder and placed in a spoon. The spoon was then heated from underneath with an open flame. Once the powder began to caramelize and smoke, the heat was removed and the powder was mixed using a metal spatula. The spoon was again heated until the powder began to caramelize further. The heat was once again removed, and the powder was allowed to cool. The resulting powders were then removed from the spoon and placed in a mortar and pestle for subsequent crushing. The comparator tablet resulted in a powder that could be easily crushed into a fine powder. Unlike the comparator tablet, the product tablet resulted in a sticky com-

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position, rendering the product tablet unsuitable for grinding into a fine powder after the crushing process.

Example 19

Separation Studies

To determine the ease at which the immediate release (IR) and extended release (ER) layers of a bilayer form of the pharmaceutical composition disclosed herein could be tampered with, several attempts were made at separating the immediate release (IR) and extended release (ER) layers of the product (as defined in Example 18). Initially, a tablet dosage form of the pharmaceutical composition of the present invention was positioned with the inscribed side facing up and cut completely through vertically. Upon slicing the tablet, observations revealed no visual distinction between the IR and ER layers. The tablet was then re-oriented and sliced from several additional angles. However, no demarcation line was observed between the IR and ER layers. Consequently, a drug abuser could not visually distinguish the IR and ER layers of the pharmaceutical composition disclosed herein by simply cutting the dosage form.

Example 20

Injectability Studies

An injectability study was conducted to determine the extent to which crushed and dissolved tablets of the pharmaceutical composition disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (the "product") could be drawn into a syringe for intravenous administration as compared to a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen that had been crushed and dissolved (the "comparator"). Intravenous administration is a common practice used by drug abusers as a means to potentiate their drugs by administering the drug as one large bolus instead of a steady release over time. Two measureable entities were evaluated: the amount of useable fluid that was harvested through the process and the concentration of oxycodone in these aliquots. This study employed a standard 1 mL insulin syringe equipped with 22-, 26-, and 30-gauge needles, which are the typical sizes of needles used by intravenous drug users.

An intact product and comparator tablet were each ground in a mortar and pestle to yield a fine powder. The powder was then placed onto a tablespoon secured to a laboratory ring stand. 3 mL of deionized water was added to the spoon and was mixed into a slurry in an attempt to dissolve the active ingredient. To enhance solubility of the drug, a butane lighter was used to uniformly heat the bottom of the spoon. When the solution began to boil slightly, heat was removed and any liquid lost was replenished. A traditional insulin syringe (1 mL) with a makeshift cotton ball filter and the various gauge needles was used to extract the resulting liquid into the syringe.

Three types of cotton filters were evaluated for use in this procedure. The first filter was a small cotton plug placed between the needle hub and barrel of the syringe. This filter clogged for all three gauges when attempts were made to draw liquid into the syringe. The second filter was formed by inserting the tip of the syringe needle into the end of a Q-tip. This second filter also prevented an appreciable amount of fluid to be drawn into the syringe. The third filter was a small piece of cotton attached to the end of the needle. The third filter was chosen for further study because it was the only

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filter evaluated in which liquid could be drawn into the syringe for all three gauges without clogging the filter. The drawn liquid was collected, measured and quantified by LC/MS/MS analysis.

When water was mixed with the ground product tablet, the solid did not completely dissolve upon heating. Instead, a pasty material was produced that did not readily disperse when mixed. The product required almost constant mixing of the crushed powder and water with constant heating to produce a removable liquid. It was difficult to generate a homogeneous mixture of liquid that could be drawn into a syringe because the combined volume of the crushed product tablet and the 3 mL of water essentially filled the spoon to capacity. Additionally, with heating, it was necessary to replenish the evaporated water to maintain a constant slurry level in the spoon. Liquid samples were drawn from the bottom of the spoon with a 1 mL syringe with the cotton plug on the tip. This study demonstrated that only about 1 mL of liquid could consistently be drawn into the syringe, independent of needle size. The resulting liquid in the syringe was murky and not transparent due to particulate matter.

In contrast, a large portion of the comparator readily dissolved when mixed and heated in the tablespoon. The resulting liquid in the syringe therefore contained much less particulate matter than the liquid resulting from the product tablet.

These results indicate that injection is not a preferred form of drug diversion for the product tablets. When adding water to the ground tablets, the user may recover only a small portion of that liquid for use in a syringe. The product tablet tended to produce a semi-solid paste that interfered with liquid recovery through the syringe. The overall results indicate a recovery of less than 20% of the oxycodone in the product tablet.

Example 21

Snorting Studies

Another method of tampering and diversion is to grind a tablet into a fine powder and insufflate (snort) the powder. The inhaled powder is deposited inside the nasal passage, and the oxycodone is absorbed through the mucous membranes of the nasal passage. In order for the procedure to work efficiently, the powder must deposit as a thin layer onto the nasal tissue in the sinus cavity. A study was performed to estimate the effectiveness of this process using the pharmaceutical composition disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (the "product") and a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the "comparator").

Product tablet and a comparator tablet were ground in a mortar and pestle. 1 mL of water was added to each ground tablet, and the resulting combination was mixed in an attempt to produce a thin slurry, which mimics the interface between the nasal passage and the absorptive tissue. The product tablet formed a paste that tended to clump. The comparator produced a more fluid consistency. Consequently, the comparator produced a more effective coating for absorption of insufflated oxycodone in the nasal cavity than the product disclosed herein.

Example 22

Dose Dumping Studies

Dose dumping is the process of releasing the active ingredient(s) of an extended release pharmaceutical formulation in

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a short period of time in a manner in which the entire dosage, or a significant portion of the dosage, becomes available for absorption in the body. This is often achieved by ingesting tablets along with alcoholic beverages to enhance drug delivery. The alcohol serves as a means to act on either the coating of a tablet to help release the active ingredients or to promote greater absorption within the body. This method is employed by drug abusers as an attempt to potentiate analgesic drugs. Release of elevated quantities of drug can lead to increased euphoric effects but can also cause adverse effects, some of which may be fatal.

Two dissolution experiments were performed in a dose dumping study. The dissolutions were designed to examine the differences between intact pharmaceutical compositions disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (the "product") and a commercially available immediate-release tablet containing 7.5 mg oxycodone/325 mg acetaminophen (the "comparator") when exposed to simulated gastric fluid dissolution media ("SGF"). The first dissolution was performed in 75 mL of SGF in the absence of vodka. The second dissolution was performed in 75 mL of a 50:50 mixture of SGF and 80-proof vodka. This was designed to measure the extent that the product and comparator may be abused by the simultaneous intake of alcohol. Both dissolutions were performed at room temperature and were mixed on a stir plate. Aliquots were removed at 0.25, 0.50, 1, 2 and 4 hours for quantification by LC/MS/MS, a summary of which is contained in Table 54 below.

TABLE 54

Mean percent recovery of oxycodone in (i) simulated gastrointestinal fluid and (ii) a solution containing 50% simulated gastric fluid and 50% 80-proof vodka.

Fluid	Intact Tablet	Mean Percent Recovery at time = t				
		0.25 hr	0.5 hr	1 hr	2 hr	4 hr
SGF	Product	15%	30%	43%	57%	80%
SGF	Comparator	104%	102%	105%	102%	100%
SGF:EtOH	Product	12%	23%	35%	46%	62%
SGF:EtOH	Comparator	101%	101%	103%	100%	102%

At the end of the four hour dissolution, the product tablets were still visible but had lost their outer coating in SGF both in the presence and absence of vodka. Addition of ethanol to the SGF produced a slight decrease in the dissolution rate of the product tablet. Comparator tablets were dissolved in SGF both in the presence and absence of vodka after five minutes. Consequently, the product tablets were resistant to dose dumping when compared to the comparator tablets.

Example 23

Clinical Evaluation of the Relative Abuse Potential of an Extended Release Formulation of Oxycodone and Acetaminophen

A study may be performed to assess the relative abuse potential of a bilayer, extended-release oral formulation disclosed herein containing 7.5 mg oxycodone/325 mg acetaminophen (see Chart One) versus an immediate release oxycodone HCl/acetaminophen tablet in non-dependent, recreational opioid users. The study will consist of a screening period, and in-clinic period, and a follow-up period.

The study will consist of seven treatment periods, each of which will involve a single treatment of one of the study medications followed by a wash-out period. Tests will be

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conducted to ensure that the subjects are not physically dependent on opioids, and that they can discriminate between the effects oxycodone versus the placebo. Upon completion, the study medications will be randomly administered as a single oral dose to each subject and consist of the following:

Group A: two tablets disclosed herein containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus two placebo tablets disclosed herein plus four placebo immediate release capsules.

Group B: four tablets disclosed herein containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus four placebo immediate release capsules.

Group C: two immediate release capsules containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus two placebo immediate release capsules plus four placebo tablets disclosed herein.

Group D: four immediate release capsules containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each plus four placebo tablets disclosed herein.

Group E: two crushed tablets disclosed herein containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each placed in four capsules plus four placebo tablets disclosed herein.

Group F: two crushed immediate release tablets containing 7.5 mg oxycodone HCl and 325 mg acetaminophen each placed in two capsules plus two placebo immediate release capsules.

Group G: four placebo tablets disclosed herein plus four placebo immediate release capsules.

Subjects will receive seven treatments according to their treatment sequence, and doses will be separated.

Example 24

Varying Polyox Grades Comprising 25% by Weight of the Extended Release Portion of Bilayer Formulations

Single layer tablet formulations containing only the extended release portion were prepared, each tablet containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for the bilayer tablet and 60% of the total oxycodone HCl for the bilayer tablet. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 25% by weight of the ER portion, and therefore, the tablet weight. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the tablet of ER portion. In a third formulation, POLYOX® N-60K was employed as the extended release component in an amount of 25% by weight of the tablet or ER portion.

Dissolution profiles for the three above-described compositions were determined in USP Type II apparatus. Six tablets of each composition were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.5° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6, hr, 8 hr, and 12 hr. The final time point for the Polyox 205 was 17 hrs; the final time point for the Polyox 1105 was 15 hrs; and the final time point for the Polyox N60k

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was 18 hrs and 40 minutes. Each sample was filtered through a 0.45 μ m filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 34 and 35, respectively. This data represents dissolution for the extended release portion with the immediate release data theoretically added. These figures demonstrate that as the average molecular weight of the POLYOX® extended release component increases, the rate of dissolution at each time point decreases. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 59%, about 56%, and about 55% acetaminophen after 15 minutes, respectively; about 63%, about 59%, and about 57% acetaminophen after 30 minutes, respectively; about 69%, about 64%, and about 61% acetaminophen after 1 hr, respectively; about 78%, about 73%, and about 67% acetaminophen after 2 hr, respectively; about 91%, about 87%, and about 76% acetaminophen after 4 hr, respectively; about 97%, about 95%, and about 84% acetaminophen after 6 hr, respectively; and about 98%, about 97%, and about 90% acetaminophen after 8 hr, respectively.

The same general trend of a decreased release rate with a higher molecular weight POLYOX® grade was also observed for the oxycodone. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 53%, about 50%, and about 48% oxycodone after 15 minutes, respectively; about 60%, about 56%, and about 53% oxycodone after 30 minutes, respectively; about 68%, about 63%, and about 59% oxycodone after 1 hr, respectively; about 80%, about 75%, and about 67% oxycodone after 2 hr, respectively; about 94%, about 91%, and about 80% oxycodone after 4 hr, respectively; about 100%, about 98%, and about 89% oxycodone after 6 hr, respectively; and about 100%, about 99%, and about 95% oxycodone after 8 hr, respectively.

Example 25

Varying Polyox Grades Comprising 45% by Weight of the Extended Release Portion of Bilayer Formulations

Single layer formulations containing only the extended release portion described herein were prepared, each tablet containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for a bilayer tablet and 60% of the total oxycodone HCl for a bilayer tablet. In a first formulation, POLYOX® 205 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a second formulation, POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a third formulation, POLYOX® N-60K was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. The other excipients in the extended release portion were microcrystalline cellulose, spress B825, citric acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate.

Dissolution profiles for the three above-described formulations were determined in USP Type II apparatus. Six tablets of each formulation were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. \pm 0.5° C. The mixture was stirred at 150 \pm 6 rpm, and the temperature was maintained at 37° C. \pm 0.5° C. through 12 hr.

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The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the Polyox 205 was 17 hours; the final time point for Polyox 1105 was 17.5 hours; and the final time point for Polyox N60k was 23.5 hours. Each sample was filtered through a 0.45 μ m filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 36 and 37, respectively. This data represents dissolution for the extended release portion with the immediate release data theoretically added. Consistent with the results of Example 24, the rate of dissolution at each time point decreases as the molecular weight of POLYOX® increases. For example, the formulations containing POLYOX® 205, 1105, and N-60K had released about 53%, about 53%, and about 53% acetaminophen after 15 minutes, respectively; about 56%, about 55%, and about 54% acetaminophen after 30 minutes, respectively; about 61%, about 60%, and about 57% acetaminophen after 1 hr, respectively; about 70%, about 67%, and about 63% acetaminophen after 2 hr, respectively; about 85%, about 81%, and about 71% acetaminophen after 4 hr, respectively; about 95%, about 90%, and about 79% acetaminophen after 6 hr, respectively; about 99%, about 95%, and about 85% acetaminophen after 8 hr, respectively; and about 99%, about 96%, and about 93% acetaminophen after 12 hr.

The formulations containing POLYOX® 205, 1105, and N-60K also released about 47%, about 47%, and about 46% oxycodone after 15 minutes, respectively; about 51%, about 50%, and about 49% after 30 minutes, respectively; about 59%, about 56%, and about 53% oxycodone after 1 hr, respectively; about 70%, about 67%, and about 62% oxycodone after 2 hr, respectively; about 88%, about 83%, and about 74% oxycodone after 4 hr, respectively; about 99%, about 93%, and about 83% oxycodone after 6 hr, respectively; and about 100%, about 97%, and about 90% oxycodone after 8 hr, respectively.

Example 26

Varying the Concentrations of a Specific Polyox Grade in the Extended Release Portion of Bilayer Formulations

The data from Examples 24 and 25 indicate that an increase in the amount of POLYOX® in the pharmaceutical composition retards the release of oxycodone and acetaminophen from the pharmaceutical composition. To confirm this observation, single layer extended release formulations described herein were prepared, each containing a total of 9 mg of oxycodone HCl and a total of 250 mg of acetaminophen. Since these tablets contained only the extended release portion, they contained 50% of the total acetaminophen for the bilayer tablet and 60% of the total oxycodone for the bilayer tablet. In a first formulation, POLYOX® 1105 was employed as the extended release component in an amount of 25% by weight of the tablet or ER portion. In a second formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 35% by weight of the tablet or ER portion. In a third formulation, POLYOX™ 1105 was employed as the extended release component in an amount of 45% by weight of the tablet or ER portion. In a fourth formulation, POLYOX® 1105 was employed as the extended release component in an amount of 55% by weight of the tablet or ER portion. The amount of the microcrystalline cellulose in the four formulations was adjusted to account for the differing amounts of POLYOX® 1105 in each formula-

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tion. The other excipients in the extended release portion were B825, citric acid anhydrous, EDTA, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate. However, the percentages for all the other excipients remained the same for each formulation, and were consistent with the percentages used in Example 25.

Dissolution profiles for the above-described formulations were determined in USP Type II apparatus. Six tablets of each formulation were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. $\pm 0.5^\circ$ C. The mixture was stirred at 150 \pm 6 rpm, and the temperature was maintained at 37° C. $\pm 0.5^\circ$ C. through 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. The final time point for the 25%, 35%, 45%, and 55% formulations was 15 hr, 15 hr, 17.5 hr, and 17.5 hr, respectively. Each sample was filtered through a 0.45 μ m filter and analyzed by HPLC using standard procedures.

The cumulative release profiles of acetaminophen and oxycodone from these compositions are shown in FIGS. 38 and 39, respectively. These profiles confirm that as the amount of POLYOX® 1105 used in the pharmaceutical formulations increase, the release rate of the acetaminophen and oxycodone generally decreases. For example, the formulations containing 25%, 45%, and 55% POLYOX® 1105 had released about 56%, about 53%, and about 53% acetaminophen after 15 minutes, respectively; about 59%, about 56%, about 55%, and about 55% acetaminophen after 30 minutes, respectively; about 64%, about 61%, about 60%, and about 59% acetaminophen after 1 hr, respectively; about 73%, about 70%, about 67%, and about 66% acetaminophen after 2 hr, respectively; about 87%, about 84%, about 81%, and about 79% acetaminophen after 4 hr, respectively; about 95%, about 93%, about 90%, and about 89% acetaminophen after 6 hr, respectively; about 97%, about 97%, about 95%, and about 95% acetaminophen after 8 hr, respectively; and about 97%, about 97%, about 96%, and about 98% acetaminophen after 12 hr, respectively.

Similar trends were observed for the cumulative release of oxycodone. However, there was no observable difference in the release of oxycodone from the formulations containing 45% and 55% POLYOX® 1105. For example, the formulations containing 25%, 45%, and 55% POLYOX® 1105 had

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released about 50%, about 47%, and about 45% oxycodone after 15 minutes, respectively; about 56%, about 51%, about 50%, and about 50% oxycodone after 30 minutes, respectively; about 63%, about 58%, about 56%, and about 56% oxycodone after 1 hr, respectively; about 75%, about 70%, about 67%, and about 66% oxycodone after 2 hr, respectively; about 91%, about 87%, about 83%, and about 82% oxycodone after 4 hr, respectively; about 98%, about 96%, about 93%, and about 93% oxycodone after 6 hr, respectively; about 99%, about 99%, about 97%, and about 98% oxycodone after 8 hr, respectively; and about 99%, about 100%, about 97%, and about 100% oxycodone after 12 hr, respectively.

Example 27

In Vitro Dissolution of Controlled-Release Bilayer Tablets Containing 7.5 mg Oxycodone and 325 mg Acetaminophen Performed at a 100 rpm Paddle Speed

Three batches of bilayer formulations described herein were prepared, each containing a total of 7.5 mg of oxycodone HCl and a total of 325 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the oxycodone HCl was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations of each batch were determined in a USP Type II apparatus. Twelve tablets from each batch were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C. $\pm 0.5^\circ$ C. The mixture was stirred at 100 \pm 4 rpm, and the temperature was maintained at 37° C. $\pm 0.5^\circ$ C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a 0.45 μ m filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and oxycodone from each batch are described in Table 55.

TABLE 55

Release rate data of bilayer tablets (7.5 mg oxycodone HCl; 325 mg acetaminophen) using a 100 rpm dissolution method.								
Time	Oxycodone HCl				Acetaminophen			
(Hours)	Mean (%)	RSD	Min (%)	Max (%)	Mean (%)	RSD	Min (%)	Max (%)
Batch 1								
0.25	31.7	2.1	30.6	32.5	51.8	1.4	50.9	53.1
0.5	37.1	1.3	36.3	37.8	54.3	1.3	53.5	55.6
1.0	45.4	1.0	44.9	46.0	58.6	1.2	57.7	60.1
2.0	58.5	1.3	57.4	59.7	66.0	1.2	64.8	67.7
4.0	78.6	1.7	76.8	80.5	78.5	1.5	77.0	80.6
6.0	92.2	1.8	90.0	94.7	88.0	1.6	86.0	90.3
8.0	99.5	1.8	97.4	102.7	93.8	1.5	91.8	96.3
12.0	101.7	1.4	99.7	104.3	96.1	1.0	94.9	98.2
Batch 2								
0.25	31.6	3.5	29.6	34.0	52.1	4.0	48.8	55.8
0.5	37.2	3.2	34.9	39.9	54.5	3.8	51.4	58.3
1.0	45.4	3.3	42.4	48.3	59.1	3.5	56.0	63.1
2.0	58.9	1.7	57.3	61.1	66.4	3.0	63.6	70.0
4.0	79.1	1.5	77.7	81.5	78.7	2.5	75.4	81.8

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TABLE 55-continued

Release rate data of bilayer tablets (7.5 mg oxycodone HCl; 325 mg acetaminophen) using a 100 rpm dissolution method.								
Time	Oxycodone HCl				Acetaminophen			
(Hours)	Mean (%)	RSD	Min (%)	Max (%)	Mean (%)	RSD	Min (%)	Max (%)
6.0	93.1	1.3	91.5	95.8	87.7	2.2	84.4	90.7
8.0	100.2	1.2	98.7	102.3	93.5	1.9	90.4	96.2
12.0	102.7	1.3	100.4	104.4	95.6	2.0	92.6	98.4
Batch 3								
0.25	30.4	1.6	29.3	31.0	52.2	2.3	49.6	54.2
0.5	35.7	1.6	34.2	36.7	54.6	2.3	52.0	56.6
1.0	43.5	1.8	42.0	45.1	58.6	2.2	56.0	60.8
2.0	56.1	1.9	54.4	58.0	65.5	2.1	63.1	68.0
4.0	75.4	1.8	73.3	77.6	77.3	2.0	74.8	80.0
6.0	88.9	1.7	86.1	91.4	86.5	2.2	83.7	90.1
8.0	97.0	1.5	94.7	99.8	93.0	2.1	90.1	96.8
12.0	100.4	1.1	98.7	102.4	96.5	1.6	93.2	98.3

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Example 28

In Vitro Dissolution of Controlled-Release Bilayer
Tablets Containing 15 mg Oxycodone and 650 mg
Acetaminophen Performed at a 150 rpm Paddle
Speed

Bilayer formulations described herein were prepared, each containing a total of 15 mg of oxycodone HCl and a total of 650 mg of acetaminophen. 50% of the acetaminophen was contained in the immediate release portion, and the other 50% was contained in the ER layer. 25% of the oxycodone HCl was contained in the immediate release portion of the formulation, and the other 75% was contained in the ER layer. POLYOX® 1105 was employed as the extended release component in an amount of 45% by weight of the ER portion.

Dissolution profiles for the formulations were determined in a USP Type II apparatus. Six tablets were weighed, placed in a sinker, and dropped into an equilibrated dissolution bath vessel containing 900 mL of (helium sparged) 0.1 N HCl heated to 37° C.±0.55° C. The mixture was stirred at 150±6 rpm, and the temperature was maintained at 37° C.±0.5° C. for 12 hr. The bath vessel was covered with a low evaporation vessel cover. Samples (5 mL) were removed at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, and 12 hr. Each sample was filtered through a 0.45 µm filter and analyzed by HPLC using standard procedures.

The cumulative percent release of acetaminophen and oxycodone from each batch are described in Table 56.

TABLE 56

Release rate data of bilayer tablets (15 mg oxycodone HCl; 325 mg acetaminophen) using a 150 rpm dissolution method.		
Time (hr)	Oxycodone HCl (%)	Acetaminophen (%)
0.25	33.7	54.4
0.50	39.0	56.5
1	47.4	60.6
2	61.4	68.1
4	81.7	81.1
6	95.2	90.8
8	101.2	96.0
12	102.3	97.6

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Example 29

Ethanol Release Testing at a 100 rpm Paddle Speed

The ethanol release studies discussed above in Example 8 were repeated, except that the solutions were stirred at a paddle speed of 100 rpm and additional aliquots were sampled at 240 min and 480 min. Tables 57, 58, 59, 60, and 61 present the percent release of OC and APAP in the presence of 0%, 5%, 10%, 20%, and 40% ethanol, respectively. FIG. 40 presents dissolution profiles for OC and FIG. 41 presents dissolution profiles for APAP in the presence of 0%, 5%, 20%, and 40% ethanol. Like the results at a paddle speed of 150 rpm, these data reveal that, for both OC and APAP, the dissolution in 5%, 20%, or 40% ethanol was either comparable or slower than the dissolution in 0% ethanol, indicating no dose dumping for this formulation.

TABLE 57

Percent Release in 0% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Minimum	Maximum	Mean	RSD	Minimum	Maximum
15	32.5	3.7	31.5	36.0	52.2	1.6	50.7	53.4
30	37.6	2.5	36.6	39.9	54.6	1.4	53.2	55.7
45	42.1	2.7	40.9	44.8	56.8	1.4	55.3	57.9
60	45.8	2.1	44.6	48.1	58.8	1.4	57.4	59.8
75	49.6	2.3	48.2	52.2	60.8	1.4	59.2	61.8
90	53.1	2.4	51.7	55.8	62.6	1.4	60.9	63.8
105	56.3	2.4	54.8	59.3	64.3	1.4	62.6	65.6
120	59.5	2.5	57.6	63.0	66.0	1.4	64.2	67.3
240	80.3	2.5	77.3	84.9	78.6	1.8	76.3	80.6
480	102.4	1.8	100.5	107.2	95.5	1.6	92.6	97.7

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TABLE 58

Percent Release in 5% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Minimum	Maximum	Mean	RSD	Minimum	Maximum
15	31.5	2.5	30.0	32.9	52.6	2.1	51.4	55.1
30	36.8	2.4	35.6	38.5	55.1	2.0	53.8	57.6
45	40.9	2.8	38.9	43.5	57.1	2.0	55.8	59.6

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TABLE 58-continued

Percent Release in 5% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini- mum	Maximum	Mean	RSD	Mini- mum	Maximum
60	44.6	3.7	42.1	48.4	58.9	2.0	57.6	61.4
75	48.0	3.6	46.0	52.6	60.7	1.9	59.4	63.2
90	51.0	3.1	49.3	55.3	62.3	1.9	61.0	64.7
105	54.3	3.2	51.8	58.6	63.9	2.0	62.6	66.4
120	57.1	3.2	54.6	61.7	65.5	1.9	64.1	67.8
240	76.6	3.2	73.8	83.0	77.2	2.1	75.5	80.6
480	99.9	2.7	95.8	106.8	94.4	1.7	92.6	98.1

TABLE 59

Percent Release in 10% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini- mum	Maximum	Mean	RSD	Mini- mum	Maximum
15	30.3	3.1	28.9	32.1	51.7	1.8	50.1	53.4
30	35.6	3.3	33.7	37.3	54.1	1.9	52.4	55.8
45	39.6	2.6	37.6	40.9	56.0	1.9	54.3	57.8
60	43.1	2.6	41.2	44.7	57.8	1.9	56.1	59.5
75	46.2	2.3	44.1	47.5	59.5	1.8	57.7	61.1
90	49.3	2.1	47.3	50.6	61.1	1.8	59.3	62.8
105	52.2	2.2	50.1	53.6	62.6	1.8	60.9	64.2
120	54.8	2.3	52.8	56.4	64.1	1.8	62.3	65.6
240	73.8	2.2	70.8	76.1	75.5	1.7	73.4	77.4
480	98.4	2.1	94.7	101.1	93.5	1.6	91.0	95.9

TABLE 60

Percent Release in 20% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini- mum	Maximum	Mean	RSD	Mini- mum	Maximum
15	28.0	6.0	23.9	30.3	50.2	5.1	43.0	53.0
30	33.6	4.5	30.7	35.6	53.4	3.1	49.5	55.9
45	37.9	2.9	35.7	39.6	55.5	2.6	52.6	57.9
60	41.2	3.1	39.2	43.2	57.3	2.3	55.1	59.8
75	44.1	2.9	42.3	46.6	59.0	2.2	57.0	61.4
90	46.5	3.5	42.7	49.1	60.5	2.1	58.6	62.9
105	49.8	2.9	48.0	52.8	61.9	2.1	60.2	64.4
120	52.2	2.8	49.9	54.8	63.3	2.0	61.7	65.9
240	72.2	2.1	69.4	74.7	76.0	1.7	74.1	78.4
480	95.7	2.3	91.7	98.7	91.9	1.7	89.3	94.6

TABLE 61

Percent Release in 40% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini- mum	Maximum	Mean	RSD	Mini- mum	Maximum
15	11.9	13.9	10.0	15.1	16.7	23.2	12.3	22.9
30	21.1	15.4	17.3	26.2	30.4	22.3	21.7	40.7
45	26.8	11.6	22.4	30.3	38.5	15.3	29.6	44.8
60	30.8	7.0	26.8	34.0	43.1	9.2	35.9	47.1
75	34.2	5.0	31.5	36.8	46.1	5.3	41.1	49.2
90	36.9	3.2	35.1	38.8	48.3	3.3	44.6	50.2

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TABLE 61-continued

Percent Release in 40% Ethanol								
Time (Min)	OC				APAP			
	Mean	RSD	Mini- mum	Maximum	Mean	RSD	Mini- mum	Maximum
105	39.6	3.3	37.3	41.2	49.8	2.4	47.3	51.3
120	41.9	3.3	39.4	44.2	51.1	2.3	48.3	52.7
240	57.0	1.8	55.7	58.9	60.8	2.0	58.9	63.6
480	80.6	1.6	78.4	83.7	77.2	1.3	75.7	78.7

All references cited herein are hereby incorporated by reference. The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that further drugs can be included, and that the shapes, components, additives, proportions, methods of formulation, and other parameters described herein can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

What is claimed:

1. A pharmaceutical composition comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof in an amount selected from the group consisting of about 1 mg, 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, and 4.0 mg; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is 325 mg and the total amount of oxycodone or a pharmaceutically acceptable salt in the composition is about 7.5 mg; and

wherein upon oral administration of a single dose of the composition to a subject, the composition provides a C_{max} for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg, a C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg, a T_{max} for oxycodone from about 2 hours to about 7 hours, and a T_{max} for acetaminophen from about 0.5 hour to about 6 hours.

2. The pharmaceutical composition of claim 1, wherein the C_{max} for oxycodone is about 0.9 ng/mL/mg to about 1.2 ng/mL/mg.

3. The pharmaceutical composition of claim 1, wherein the C_{max} for oxycodone is about 1.0 ng/mL/mg to about 1.5 ng/mL/mg.

4. The pharmaceutical composition of claim 1, wherein the C_{max} for acetaminophen is about 6.5 ng/mL/mg to about 8.5 ng/mL/mg.

5. The pharmaceutical composition of claim 1, wherein the C_{max} for acetaminophen is about 6.0 ng/mL/mg to about 9 ng/mL/mg.

6. The pharmaceutical composition of claim 1, wherein the T_{max} for oxycodone is about 3.0 hours to about 6.0 hours.

7. The pharmaceutical composition of claim 1, wherein the T_{max} for acetaminophen is about 0.75 hours to about 1.5 hours.

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8. The pharmaceutical composition of claim 1, wherein upon oral administration of a single dose of the composition to a subject, the composition produces a blood plasma profile characterized by a AUC for oxycodone from about 9.0 ng·hr/mL/mg to about 18.5 ng·hr/mL/mg and a AUC for acetaminophen from about 35.0 ng·hr/mL/mg to about 80.0 ng·hr/mL/mg.

9. The pharmaceutical composition of claim 8, wherein the AUC for oxycodone is about 11.0 ng·hr/mL/mg to about 17.0 ng·hr/mL/mg.

10. The pharmaceutical composition of claim 8, wherein the AUC for acetaminophen is about 40.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg.

11. The pharmaceutical composition of claim 1, wherein the composition is in the form of a bilayer tablet.

12. The pharmaceutical composition of claim 11, wherein a single dose comprises two bilayer tablets.

13. A pharmaceutical composition comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof in an amount selected from the group consisting of about 1 mg, 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, and 4.0 mg; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is 325 mg and the total amount of oxycodone or a pharmaceutically acceptable salt in the composition is about 7.5 mg; and

wherein upon oral administration of multiple doses of the composition to a subject, the composition produces a blood plasma profile characterized by a mean AUC for oxycodone from about 9.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, a mean AUC for acetaminophen from about 35.0 ng·hr/mL/mg to about 80.0 ng·hr/mL/mg, a C_{max} for oxycodone from about 1.5 ng/mL/mg to about 2.0 ng/mL/mg, and a C_{max} for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg.

14. The pharmaceutical composition of claim 13, wherein the C_{max} for oxycodone is about 1.5 ng/mL/mg to about 2.0 ng/mL/mg.

15. The pharmaceutical composition of claim 13, wherein the C_{max} for acetaminophen is about 6.5 ng/mL/mg to about 8.5 ng/mL/mg.

16. The pharmaceutical composition of claim 13, wherein upon oral administration of multiple doses of the composition to a subject, the composition produces a blood plasma profile characterized by a T_{max} for oxycodone of about 3.0 hours to about 6 hours.

17. The pharmaceutical composition of claim 13, wherein upon oral administration of multiple doses of the composition to a subject, the composition produces a blood plasma profile characterized by a T_{max} for acetaminophen of about 0.75 hours to about 1.5 hours.

18. The pharmaceutical composition of claim 13, wherein the AUC for oxycodone is about 13.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg and the AUC for acetaminophen is about 35.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg.

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19. The pharmaceutical composition of claim 13, wherein the extended release component comprises polyethylene oxide.

20. The pharmaceutical composition of claim 19, wherein the polyethylene oxide has a molecular weight from about 500,000 Daltons to about 10,000,000 Daltons.

21. The pharmaceutical composition of claim 13, wherein the extended release component comprises a polymer selected from the group consisting of linear, branched, dendrimeric, or star polymers, hydrophilic polymers, and mixtures thereof

22. The pharmaceutical composition of claim 13, wherein the composition may be administered without regard to food.

23. A pharmaceutical composition comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof in an amount selected from the group consisting of about 1 mg, 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, and 4.0 mg; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is about 325 mg and the total amount of oxycodone or a pharmaceutically acceptable salt in the composition is about 7.5 mg;

wherein upon oral administration of the composition, the composition provides an $AUC_{0-1.7h}$ for acetaminophen of about 5.0 ng·h/mL/mg to about 13.0 ng·h/mL/mg; an $AUC_{1.7-4.8h}$ for acetaminophen of about 25.0 ng·h/mL/mg to about 75.0 ng·h/mL/mg, an $AUC_{0-2.8h}$ for oxycodone of about 1.0 ng·h/mL/mg to about 3.0 ng·h/mL/mg; and $AUC_{2.8-4.8h}$ of about 7.5 ng·h/mL/mg to about 15.0 ng·h/mL/mg.

24. The pharmaceutical composition of claim 23, wherein the AUC_{0-1hr} for acetaminophen is from about 1.25 ng·hr/mL/mg to about 3.25 ng·hr/mL/mg.

25. The pharmaceutical composition of claim 23, wherein the AUC_{0-2hr} for acetaminophen is from about 4.25 ng·hr/mL/mg to about 8.75 ng·hr/mL/mg.

26. The pharmaceutical composition of claim 23, wherein the AUC_{0-4hr} for acetaminophen is from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg.

27. The pharmaceutical composition of claim 23, wherein the AUC_{0-1hr} for oxycodone is from about 0.10 ng·hr/mL/mg to about 0.45 ng·hr/mL/mg.

28. The pharmaceutical composition of claim 23, wherein the AUC_{0-2hr} for oxycodone is from about 0.65 ng·hr/mL/mg to about 1.35 ng·hr/mL/mg.

29. The pharmaceutical composition of claim 23, wherein the AUC_{0-4hr} for oxycodone is from about 2.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg.

30. A pharmaceutical composition as a solid oral dosage form comprising:

(a) at least one immediate release portion comprising about 125 mg to about 325 mg of acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof in an amount selected from the group consisting of about 1 mg, 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4

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mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, and 4.0 mg; and

(b) at least one extended release portion comprising about 125 mg to about 325 mg of acetaminophen and about 4.5 mg to about 6.5 mg oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the composition is about 325 mg and the total amount of oxycodone or a pharmaceutically acceptable salt in the composition is about 7.5 mg;

wherein upon oral administration of two solid oral dosage forms of the composition in an amount of about 15 mg of oxycodone or a pharmaceutically acceptable salt thereof and about 650 mg of acetaminophen, the composition provides an $AUC_{0-1.7h}$ for acetaminophen of about 5.0 ng·h/mL/mg to about 13.0 ng·h/mL/mg; an $AUC_{1.7-48h}$ for acetaminophen of about 25.0 ng·h/mL/mg to about 75.0 ng·h/mL/mg, an $AUC_{0-2.8h}$ for oxycodone of about 1.0 ng·h/mL/mg to about 3.0 ng·h/mL/mg; and $AUC_{2.8-48h}$ of about 7.5 ng·h/mL/mg to about 15.0 ng·h/mL/mg.

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EXHIBIT F

US007976870B2

(12) **United States Patent**
Berner et al.(10) **Patent No.:** **US 7,976,870 B2**
(45) **Date of Patent:** **Jul. 12, 2011**(54) **GASTRIC RETENTIVE ORAL DOSAGE FORM WITH RESTRICTED DRUG RELEASE IN THE LOWER GASTROINTESTINAL TRACT**(75) Inventors: **Bret Berner**, Half Moon Bay, CA (US);
Jenny Louie-Helm, Fremont, CA (US);
John W. Shell, Hillsborough, CA (US)(73) Assignee: **Depomed, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 2045 days.

(21) Appl. No.: **10/769,574**(22) Filed: **Jan. 29, 2004**(65) **Prior Publication Data**

US 2004/0185105 A1 Sep. 23, 2004

Related U.S. Application Data

(60) Division of application No. 10/024,932, filed on Dec. 18, 2001, now abandoned, which is a continuation-in-part of application No. 10/045,816, filed on Oct. 25, 2001, now abandoned.

(51) **Int. Cl.****A61K 9/22** (2006.01)**A61K 9/20** (2006.01)**A61K 9/32** (2006.01)(52) **U.S. Cl.** **424/468; 424/464; 424/486**(58) **Field of Classification Search** **424/400, 424/469, 464, 468, 486**

See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**

4,434,153 A 2/1984 Urquhart et al.
 4,690,824 A 9/1987 Powell et al.
 4,695,467 A 9/1987 Uemura et al.
 4,748,023 A 5/1988 Tamás et al.
 4,753,801 A 6/1988 Ören et al.
 4,786,503 A 11/1988 Edgren et al.
 4,839,177 A 6/1989 Colombo et al.
 4,851,232 A 7/1989 Urquhart et al.
 4,865,849 A 9/1989 Conte et al.
 4,871,548 A 10/1989 Edgren et al.
 4,910,021 A 3/1990 Davis et al.
 5,002,772 A 3/1991 Curatolo et al.
 5,007,790 A 4/1991 Shell
 5,064,656 A 11/1991 Gergely et al.
 5,085,865 A 2/1992 Nayak
 5,213,808 A 5/1993 Bar-Shalom et al.
 5,232,704 A 8/1993 Franz et al.
 5,382,435 A 1/1995 Geary et al. 424/489
 5,393,765 A 2/1995 Infeld et al.
 5,422,123 A 6/1995 Conte et al.
 5,425,950 A 6/1995 Dandiker et al.
 5,458,887 A 10/1995 Chen et al.
 5,458,888 A 10/1995 Chen
 5,464,633 A 11/1995 Conte et al.
 5,472,708 A 12/1995 Chen
 5,487,901 A 1/1996 Conte et al.
 5,508,040 A 4/1996 Chen

5,549,913 A 8/1996 Colombo et al.
 5,582,837 A 12/1996 Shell
 5,609,590 A 3/1997 Herbig et al.
 5,626,874 A 5/1997 Conte et al.
 5,650,169 A 7/1997 Conte et al.
 5,651,985 A 7/1997 Penners et al.
 5,681,583 A 10/1997 Conte et al.
 5,688,776 A 11/1997 Bauer et al.
 5,736,159 A 4/1998 Chen et al.
 5,738,874 A 4/1998 Conte et al.
 5,780,057 A 7/1998 Conte et al.
 5,783,212 A 7/1998 Fasshi et al.
 5,811,126 A 9/1998 Krishnamurthy
 5,837,379 A 11/1998 Chen et al.
 5,840,329 A 11/1998 Bai
 5,840,332 A 11/1998 Lerner et al.
 5,861,173 A 1/1999 Nishioka et al.
 5,891,474 A 4/1999 Buseti et al.
 5,897,874 A 4/1999 Stevens et al.
 5,916,595 A 6/1999 Chen et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CA 2143500 8/1995

(Continued)

OTHER PUBLICATIONS

CIPRO (ciprofloxacin hydrochloride) Tablets, CIPRO (ciprofloxacin) 5% and 10% Oral Suspension Drug Information Sheet, Aug. 20, 2000, pp. 1-9.*

Ciprofloxacin. Datasheet [online]. MedSafe Information for Health Professionals, 2008 [retrieved on Jan. 14, 2010]. Retrieved from the Internet: <URL:http://www.medsafe.govt.nz/Profs/Datasheet/c/Ciproxinhocotic.htm>, pp. 1-10.*

Prostatitis. Datasheet [online]. WebMD, 2005 [retrieved on Jan. 14, 2010]. Retrieved from the Internet: <URL:http://men.webmd.com/prostatitis>, pp. 1-4.*

(Continued)

Primary Examiner — Johann R Richter*Assistant Examiner* — Andriae M Holt(74) *Attorney, Agent, or Firm* — Paul B. Simboli; Judy M. Mohr; Susan L. Harlocker(57) **ABSTRACT**

Controlled release oral dosage forms are provided for the continuous, sustained administration of a pharmacologically active agent to the upper gastrointestinal tract of a patient in whom the fed mode as been induced. The majority of the agent is delivered, on an extended release basis, to the stomach, duodenum and upper regions of the small intestine, with drug delivery in the lower gastrointestinal tract and colon substantially restricted. The dosage form comprises a matrix of a biocompatible, hydrophilic, erodible polymer with an active agent incorporated therein, wherein the polymer is one that both swells in the presence of water and gradually erodes over a time period of hours, with swelling and erosion commencing upon contact with gastric fluid, and drug release rate primarily controlled by erosion rate.

23 Claims, 9 Drawing Sheets

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U.S. PATENT DOCUMENTS

5,945,125	A	8/1999	Kim
5,972,389	A	10/1999	Shell et al.
6,027,748	A	2/2000	Conte et al.
6,033,685	A	3/2000	Qiu et al.
6,093,420	A	7/2000	Baichwal
6,120,803	A	9/2000	Wong et al.
6,207,197	B1	3/2001	Illum et al.
6,221,395	B1	4/2001	Maggi et al.
6,248,363	B1	6/2001	Patel et al.
6,261,601	B1	7/2001	Talwar et al.
6,340,475	B2	1/2002	Shell et al.
6,368,628	B1	4/2002	Seth
6,451,808	B1	9/2002	Cowles
6,488,962	B1	12/2002	Berner et al.
6,562,375	B1	5/2003	Sako et al.
2001/0018070	A1	8/2001	Shell et al.
2003/0091630	A1	5/2003	Louie-Helm et al.
2003/0133985	A1	7/2003	Louie-Helm et al.
2003/0152622	A1	8/2003	Louie-Helm et al.
2004/0156899	A1	8/2004	Louie-Helm et al.

FOREIGN PATENT DOCUMENTS

EP	0795324	A2	9/1997
EP	0598309	B1	1/1998
GB	1330829		9/1973
WO	WO 9626717	A1 *	9/1996
WO	WO 96/32097	A1	10/1996
WO	WO 98/55107	A1	12/1998
WO	WO 00/23045	A1	4/2000
WO	WO 00/38650	A1	7/2000
WO	WO 01/32217	A3	5/2001
WO	WO 01/56544	A3	8/2001
WO	WO 01/97783	A1	12/2001
WO	WO 02/083687	A1	10/2002

OTHER PUBLICATIONS

Ciprofloxacin Patient Information Sheet, Patient Information Sheet. [online]. Preferred Pharmaceuticals, 2000 [retrieved on Jul. 30, 2010]. Retrieved from the Internet: <URL: <http://www.preferredpharmaceuticals.com/PEI/Ciprofloxacin.pdf>>*

Hou et al., "Gastric Retentive Dosage Forms: A Review," *Crit. Rev. Ther. Drug Carrier Syst.* (2003) 20(6):461-497.

Louie-Helm et al., "Pharmacokinetics of Ciprofloxacin Gastric Retentive Tablets in Healthy Volunteers," *Control Release Soc. 28th An. Meeting Proc.* (2001) 6044.

Bloem et al., "A controlled trial of a slow-release form of furosemide in hypertension," *Curr. Ther. Res.* (1981) 29:577-583.

Boles Ponto et al., "Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review," (Parts I and II), *Clin. Pharmacokinetics* (1990) 18:381-471.

Gabr et al., "Formulation and evaluation of buffered floating furosemide delivery systems," *S.T.P. Pharma Sci.* (2000) 10:181-186.

Iannuccelli et al., "PVP solid dispersions for the controlled release of furosemide from a floating multiple-dose unit system," *Drug Dev. Indus. Pharm.* (2000) 26:595-603.

Kaniwa et al., "The bioavailability of flufenamic acid and its dissolution rate from capsules," *Intl. J. Clin. Pharmacol., Ther. Toxicol.* (1983) 21:56-63.

Menon et al., "Development and evaluation of a monolithic floating dosage form for furosemide," *J. Pharmac. Sci.* (1994) 83:239-245.

Uchino et al., "Clinical pharmacokinetics and diuretic effect of furosemide in plain tablet and retard capsule with normal subjects and cirrhotic patients," *J. Pharm. Dyn.* (1983) 6:684-691.

Wakelkamp et al., "The influence of frusemide formulation on diuretic effect and efficiency," *J. Clin. Pharmacol.* (1999) 48:361-366.

Abrahamsson et al. (1993), "Absorption, Gastrointestinal Transit, and Tablet Erosion of Felodipine Extended-Release (ER) Tablets," *Pharmaceutical Research* 10(5):709-714.

Apicella et al. (1993), "Poly(ethylene oxide) (PEO) and Different Molecular Weight PEO Blends Monolithic Devices for Drug Release," *Biomaterials* 14(2):83-90.

Columbo et al. (1990), "Drug Release Modulation by Physical Restrictions of Matrix Swelling," *International Journal of Pharmaceutics* 63:43-48.

Conte et al. (1996), "Modulation of the Dissolution Profiles from Geomatrix® Multi-Layer Matrix Tablets Containing Drugs of Different Solubility," *Biomaterials* 17(9):889-896.

U.S. Appl. No. 09/425,491, filed Oct. 22, 1999, Shell et al.

U.S. Appl. No. 10/045,823, filed Oct. 25, 2001, Gusler et al.

U.S. Appl. No. 10/045,823, filed Nov. 6, 2001, Shell et al.

U.S. Appl. No. 10/066,146, filed Feb. 1, 2002, Lim et al.

U.S. Appl. No. 10/152,914, filed May 20, 2002, Fara et al.

Davis et al. (1986), "The Effect of Density on the Gastric Emptying of Single- and Multiple-Unit Dosage Forms," *Pharmaceutical Research* 3(4):208-213.

Deshpande et al. (1997), "Development of a Novel Controlled-Release System for Gastric Retention," *Pharmaceutical Research* 14(6):815-819.

Gusler et al. (Jun. 2001), "Pharmacokinetics of Metformin Gastric-Retentive Tablets in Healthy Volunteers," *The Journal of Clinical Pharmacology* 41(6):655-661.

Huber et al. (1966), "Utilization of Hydrophilic Gums for the Control of Drug Release from Tablet Formulations. I. Disintegration and Dissolution Behavior," *Journal of Pharmaceutical Sciences* 55(9):974-976.

Hwang et al. (1998), "Gastric Retentive Drug-Delivery Systems," *Critical Reviews in Therapeutic Drug Carrier Systems* 15(3):243-284.

Katori et al. (1995), "Estimation of Agitation Intensity in the GI Tract in Humans and Dogs Based on in Vitro/in Vivo Correlation," *Pharmaceutical Research* 12(2):237-243.

Kim (1995), "Drug Release from Compressed Hydrophilic POLYOX-WSR Tablets," *Journal of Pharmaceutical Sciences* 84(3):303-306.

Korsmeyer et al. (1983), "Mechanisms of Solute Release from Porous Hydrophilic Polymers," *International Journal of Pharmaceutics* 15:25-35.

Lapidus et al. (1966), "Some Factors Affecting the Release of a Water-Soluble Drug from a Compressed Hydrophilic Matrix," *Journal of Pharmaceutical Sciences* 55(8):840-843.

Maggi et al. (2000), "Highly Swellable, Multi-Layer Tablets to Prolong the Residence Time of the Delivery Device in the Stomach," *Abstracts /Journal of Controlled Release* 64:333-334.

Maggi et al. (2000), "High Molecular Weight Polyethylene Oxides (PEOs) as an Alternative to HPMC in Controlled Release Dosage Forms," *International Journal of Pharmaceutics* 195:229-238.

Rao et al. (1988), "Swelling Controlled-Release Systems: Recent Developments and Applications," *International Journal of Pharmaceutics* 48:1-13.

Reynolds et al. (1998), "Polymer Erosion and Drug Release Characterization of Hydroxypropyl Methylcellulose Matrices" *Journal of Pharmaceutical Sciences* 87(9):1115-1123.

Shameem et al. (1995), "Oral Solid Controlled Release Dosage Forms: Role of GI-Mechanical Destructive Forces and Colonic Release in Drug Absorption Under Fasted and Fed Conditions in Humans," *Pharmaceutical Research* 12(7):1049-1054.

Siepmann et al. (1999), "A New Model Describing the Swelling and Drug Release Kinetics from Hydroxypropyl Methylcellulose Tablets," *Journal of Pharmaceutical Sciences* 88(1):65-72.

Yang et al. (1996), "Zero-Order Release Kinetics from a Self-Correcting Floatable Asymmetric Configuration Drug Delivery System," *Journal of Pharmaceutical Sciences* 85(2):170-173.

DOW Chemical U.S.A. Product Information Publication, "Formulating for Controlled Release with METHOCCEL Cellulose Ethers", 34 pages (Oct. 5, 2007).

* cited by examiner

FIG. 1 - In Vitro Release Profiles of Ciprofloxacin from IR and GR-1 Tablets

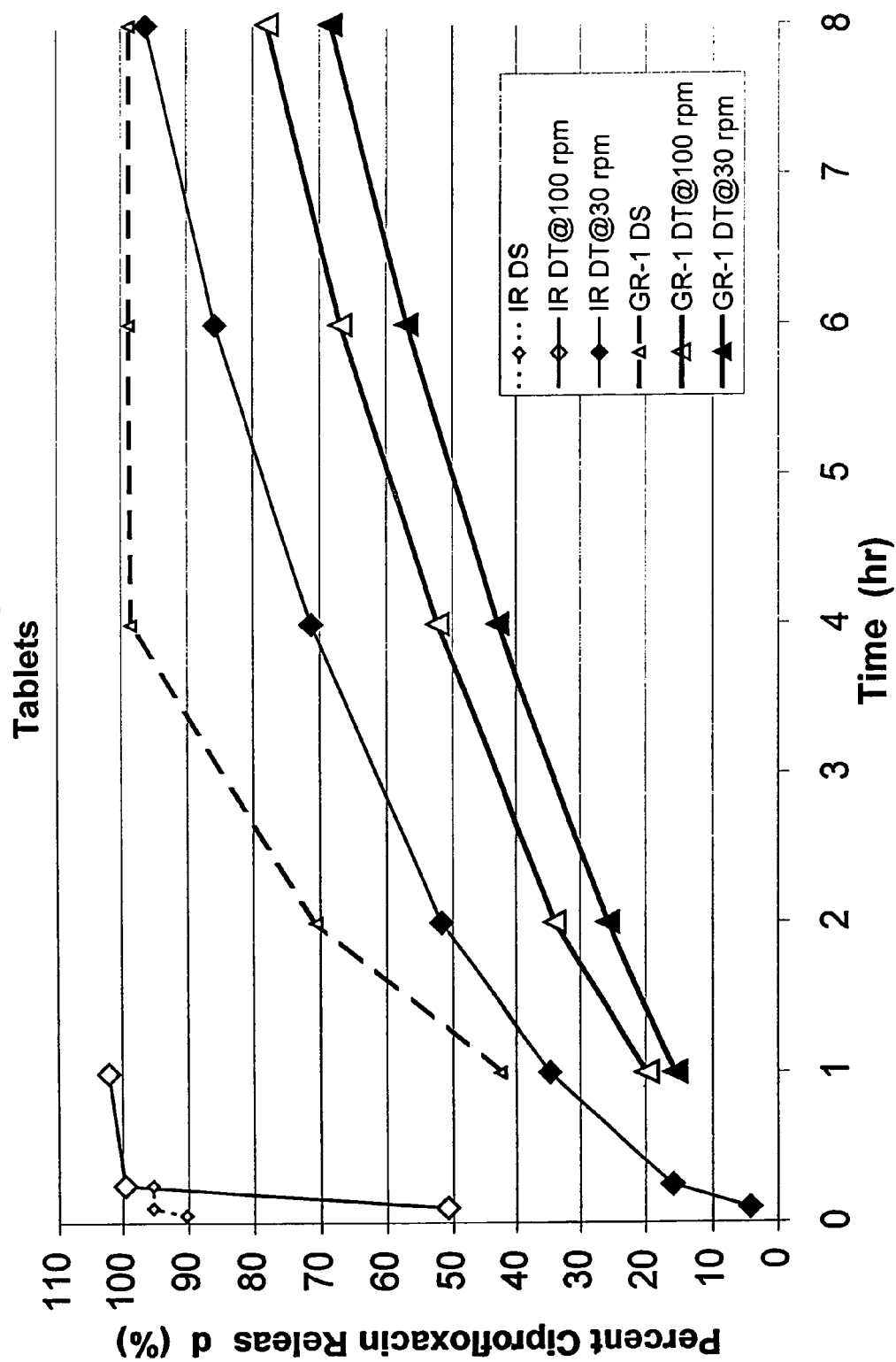
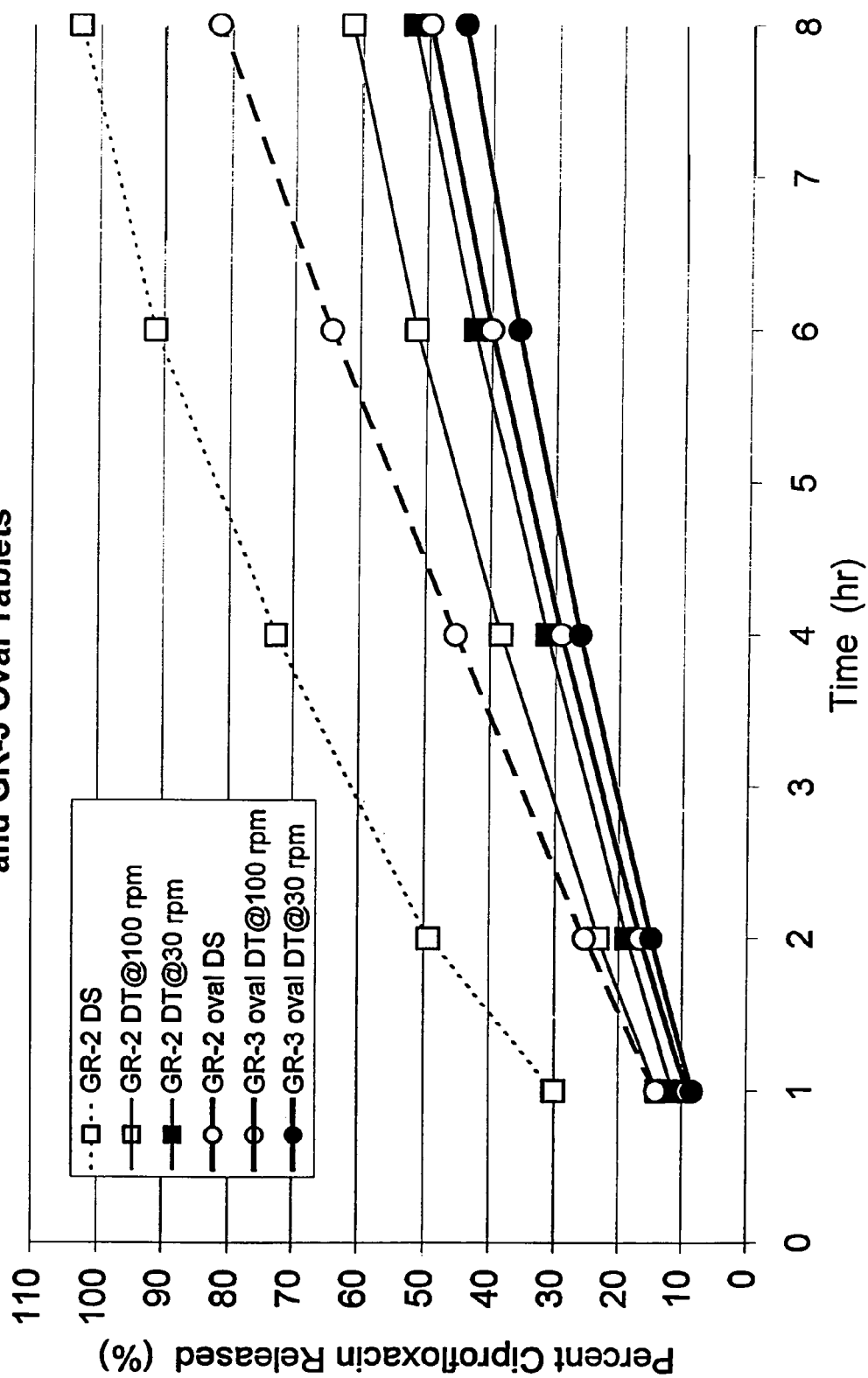


FIG. 2 - In Vitro Release Profiles of Ciprofloxacin from GR-2 Caplet and GR-3 Oval Tablets



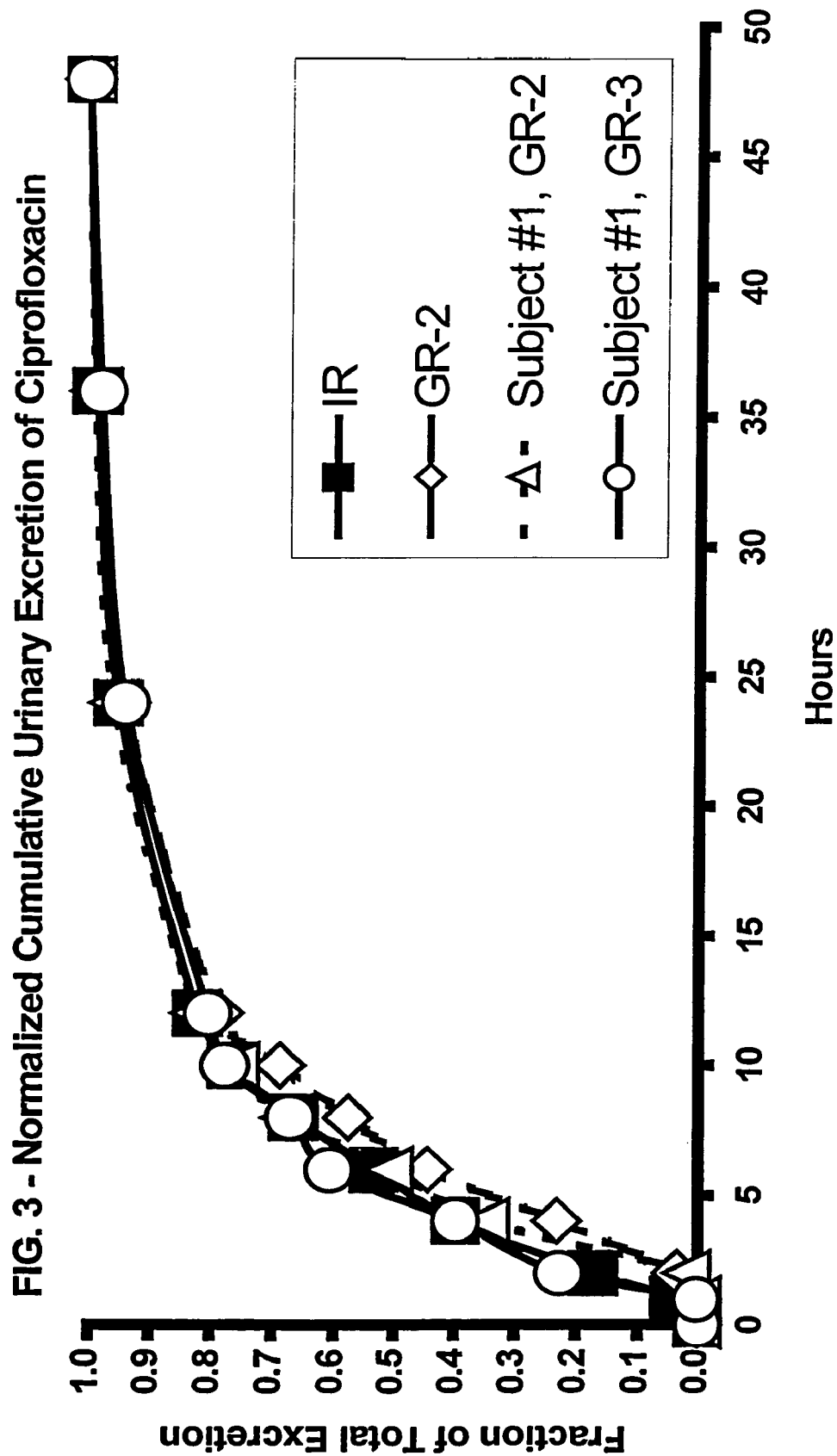
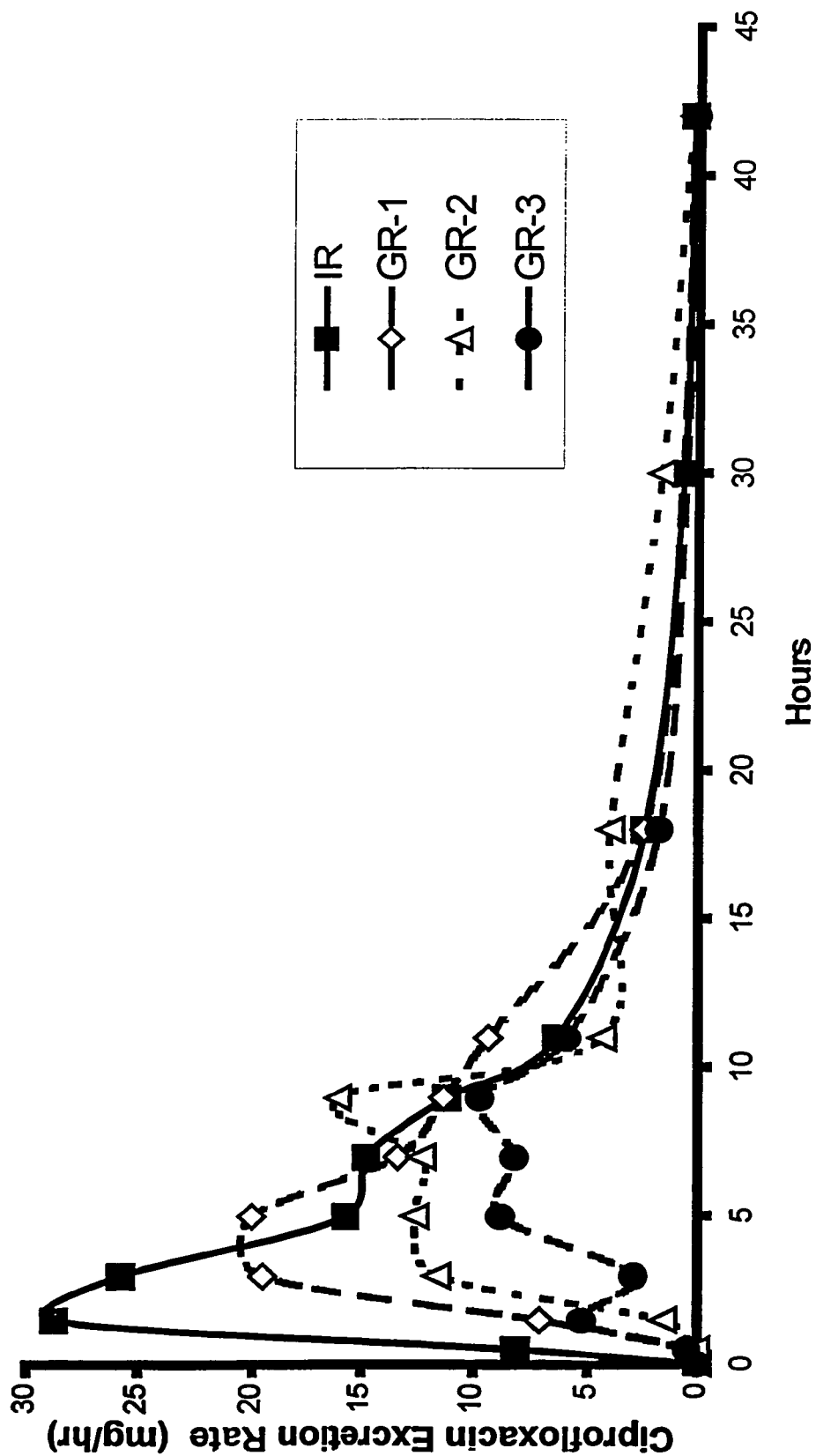


FIG. 4 - Urinary Excretion Rate of Ciprofloxacin

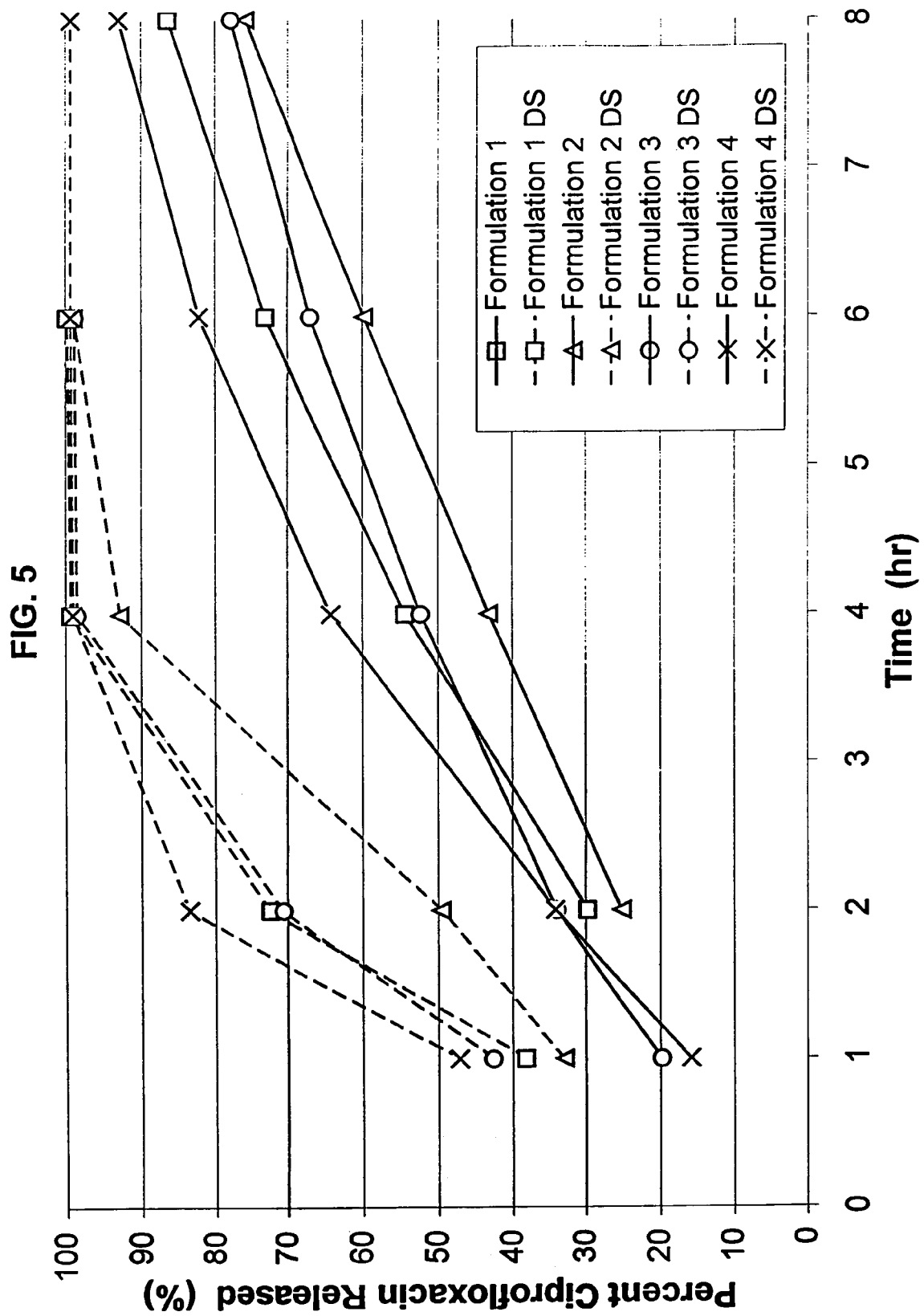


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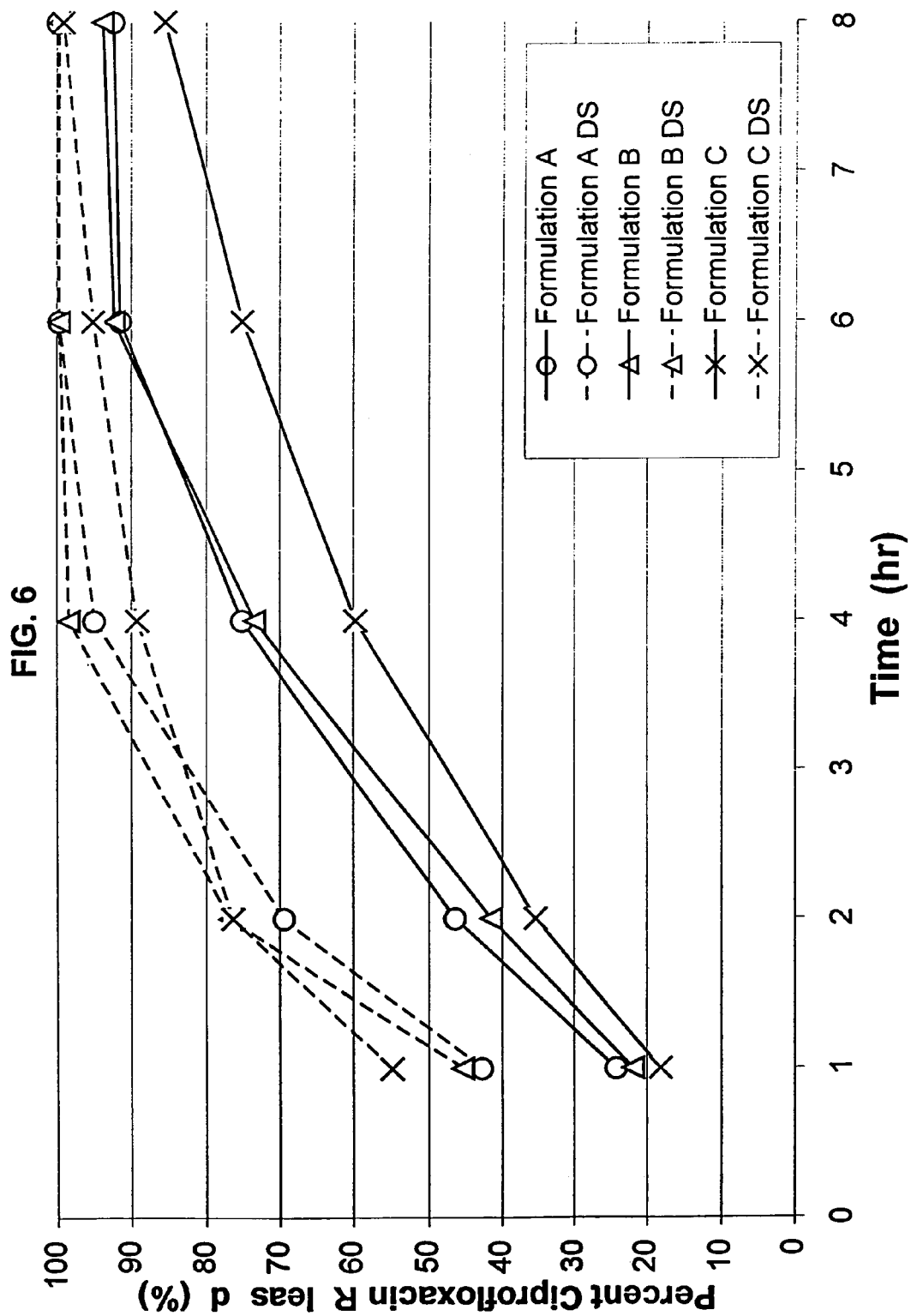


FIG. 7 - In Vitro Dissolution and Disintegration Release Profiles

(pH=1)

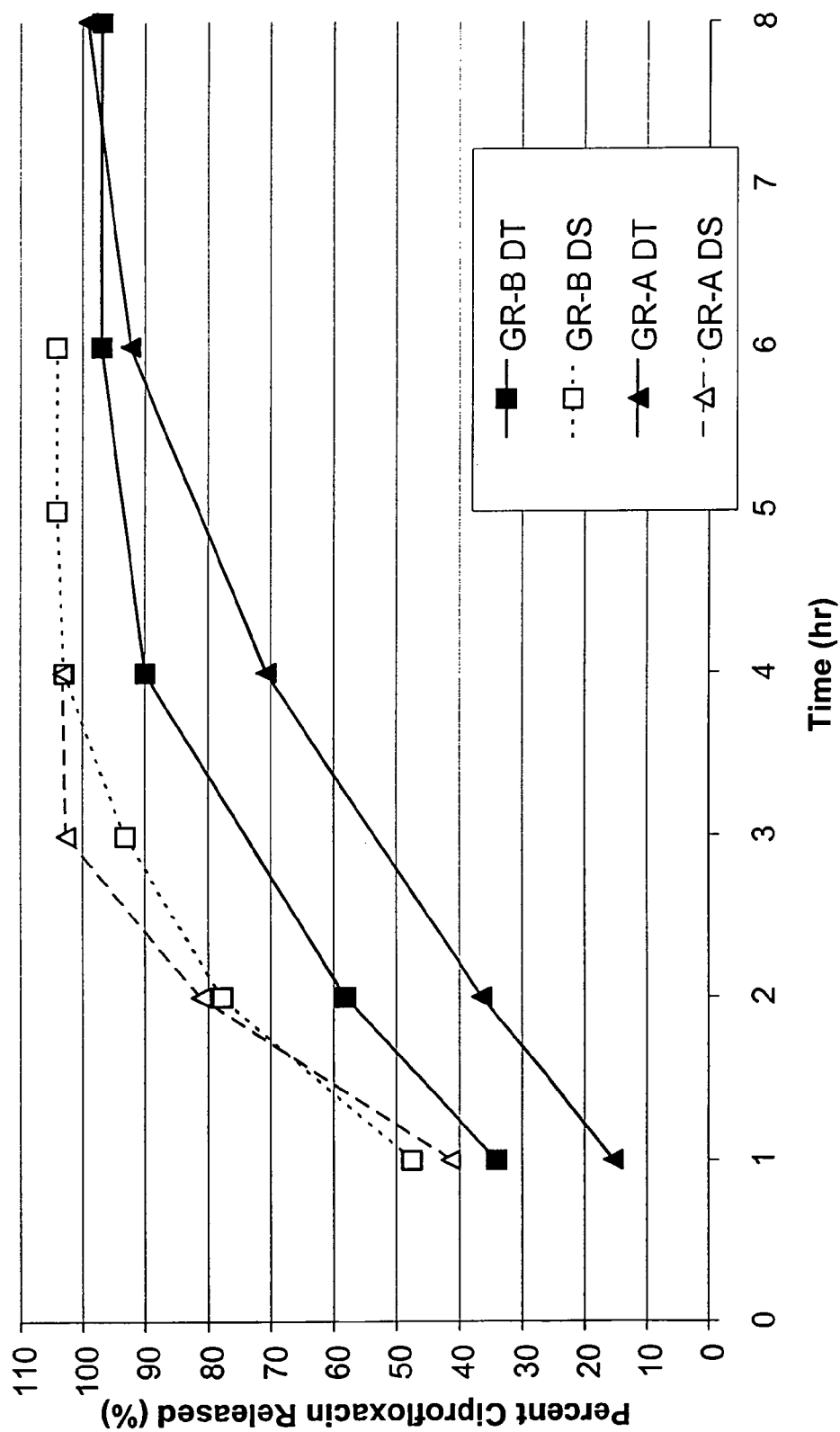


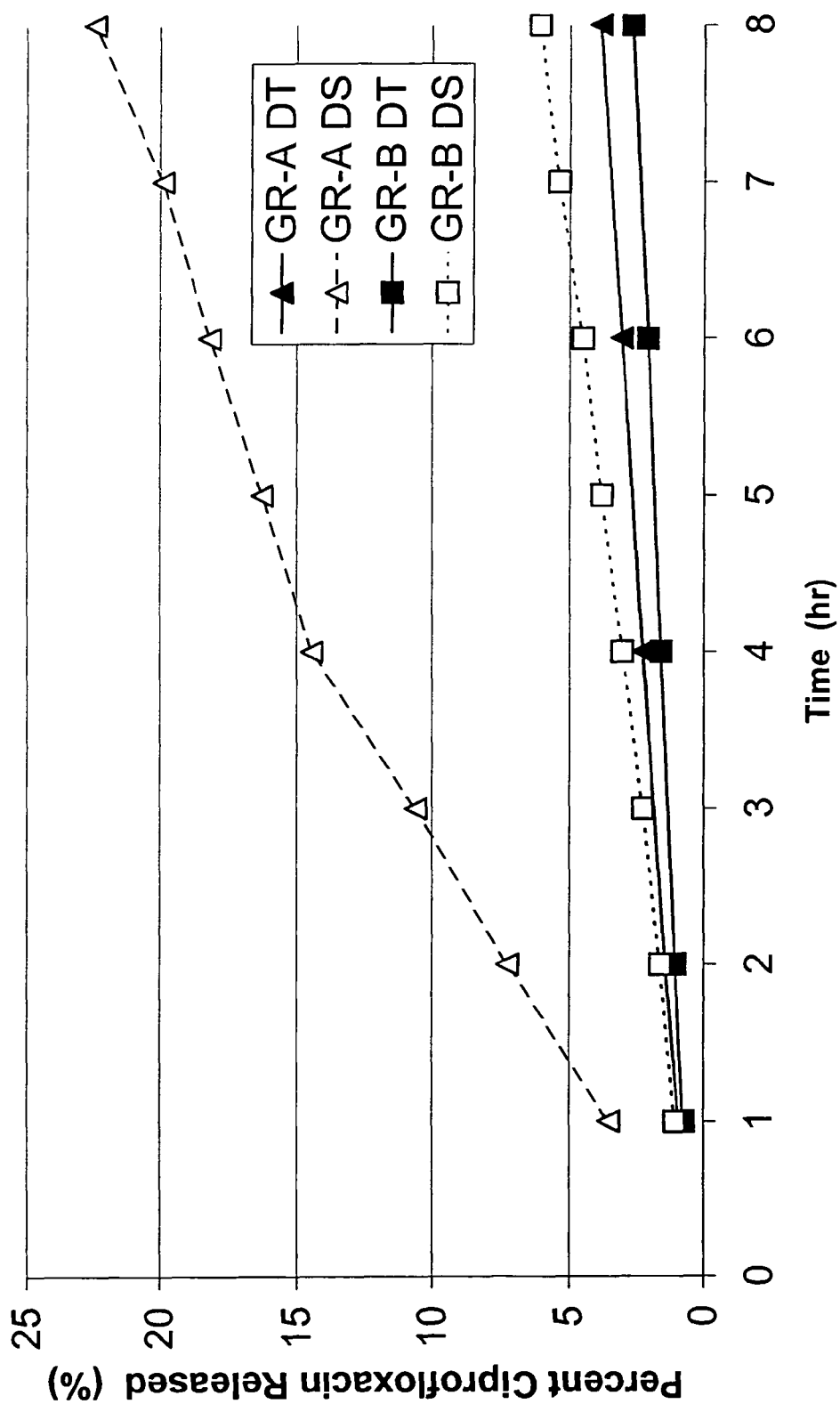
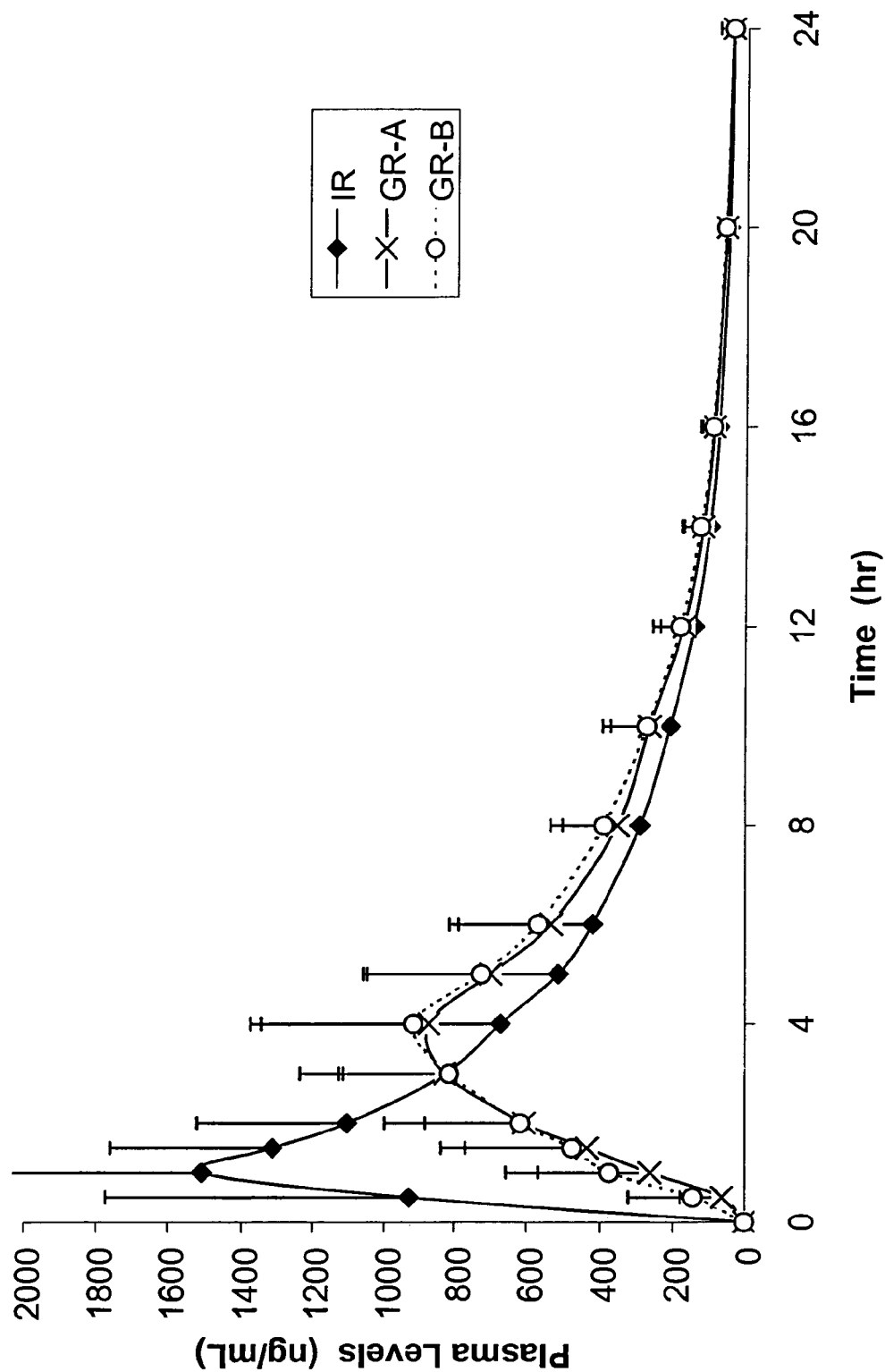
FIG. 8 - Ciprofloxacin Release into pH 6.8 Buffer

FIG. 9 - Ciprofloxacin 500 mg: GR vs. IR in Fed Mode

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GASTRIC RETENTIVE ORAL DOSAGE FORM WITH RESTRICTED DRUG RELEASE IN THE LOWER GASTROINTESTINAL TRACT

CROSS REFERENCE TO RELATED APPLICATION

This is a divisional of U.S. patent application Ser. No. 10/024,932, filed Dec. 18, 2001, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 10/045,816, filed on Oct. 25, 2001 now abandoned, the disclosures of which are hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates generally to the field of drug delivery. More particularly, the invention relates to controlled release, gastric retentive dosage forms for oral administration, formulated so as to deliver the majority of the incorporated drug into the stomach and upper gastrointestinal tract, with restricted drug delivery in the lower gastrointestinal tract.

BACKGROUND OF THE INVENTION

Sustained release dosage forms for oral administration, designed to deliver a pharmacologically active agent over an extended time period, are well known. In particular, dosage forms that are capable of delivering drug to the stomach and gastrointestinal tract in a controlled, "sustained release" manner are described in U.S. Pat. Nos. 5,007,790 to Shell, 5,582, 837 to Shell and 5,972,389 to Shell et al., all of common assignment herewith. The dosage forms described in the aforementioned patents are comprised of particles of a hydrophilic, water-swallowable polymer with the drug dispersed therein. The polymeric particles in which the drug is dispersed absorb water, causing the particles to swell, which in turn promotes their retention in the stomach and also allows the drug contained in the particles to dissolve and then diffuse out of the particles. The polymeric particles also release drug as a result of physical erosion, i.e., degradation.

Release of certain types of pharmacologically active agents or fragments thereof into the lower gastrointestinal tract is not desirable and may be detrimental to a number of patients. Release of antibiotics into the colon, for example, may disrupt the delicate balance of the natural flora and result in conditions such as pseudomembranous colitis. Most oral dosage forms, especially controlled release dosage forms, have the potential to deliver a significant amount of drug to the lower gastrointestinal tract and colon.

It has now been discovered that erodible, swellable dosage forms akin to those described in the '790, '837 and '389 patents may be modified so that drug delivery is targeted, i.e., the active agent is primarily released in the stomach and upper gastrointestinal tract, while release in the lower gastrointestinal tract and colon is minimal.

Representative active agents with which the present invention may be used are fluoroquinolone antibiotics, i.e., fluorinated analogs of nalidixic acid. These antibiotics are active against both gram-positive and gram-negative bacteria, and are believed to exert their therapeutic effect by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, thus blocking bacterial DNA synthesis. Fluoroquinolone antibiotics include ciprofloxacin, clinafloxacin, enoxacin, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin,

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moxifloxacin, norfloxacin, ofloxacin, pefloxacin, sparfloxacin, trovafloxacin, and acid addition salts thereof.

Ciprofloxacin, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, is available commercially from the Bayer Corporation under the trade name Cipro®. Ciprofloxacin is of particular current interest, not only for its utility in treating opportunistic bacterial infections associated with HIV (e.g., infection with mycobacterium avium complex, or "MAC"), urinary tract infections (including those caused by multi-drug resistant bacteria such as *Pseudomonas*), bacterial diarrhea (caused, for example, by *Shigella*, *Salmonella*, toxigenic *E. coli*, or *Campylobacter*), tissue, bone and joint infections (e.g., caused by organisms such as *Enterobacter*), but also for its utility in inhibiting *Bacillus anthracis*, commonly known as "anthrax." See, for example, D'iakov et al. (1994), "Comparative Evaluation of the Effectiveness of Fluoroquinolones in Experimental Anthrax Infection," *Antibiot. Khimioter.* 39(6):15-19; Friedlander et al. (1993), "Postexposure Prophylaxis Against Experimental Inhalation Anthrax," *J. Infect. Dis.* 167(5):1239-1243; Kelly et al. (1992) *J. Infect. Dis.* 166(5): 1184-1187. Ciprofloxacin is rapidly and well absorbed from the gastrointestinal (G.I.) tract, with an absolute bioavailability in the range of approximately 55% to 85%, typically around 70%. With the presently available immediate release dosage form, the maximum serum concentration is attained 1-2 hours after dosing and the serum half-life is approximately 4 hours. Ciprofloxacin and associated uses, synthetic methods, and formulations are described in U.S. Pat. Nos. 4,670,444, 4,705,789, 4,808,583, 4,844,902, 4,957,922, 5,286,754, 5,695,784, and 6,136,347.

The current ciprofloxacin dosage forms are administered once every twelve hours. Since the effect of ciprofloxacin persists longer than the 4-hour half-life of the drug (Davis et al. (1996) *Drugs* 51:1019-1074), extension of the duration of the plasma profile should, in theory, enable once daily delivery. However, design of a once daily dosage form with conventional sustained release dosage forms is problematic, because ciprofloxacin is poorly absorbed in the colon (Arder et al. (1990) *Br. J. Clin. Pharmacol.* 30:35-39) and delivery of any antibiotic to a healthy colon may lead to enterocolitis (Schacht et al. (1988) *Infection* 16:S29), as alluded to above.

There is accordingly a need in the art to provide gastric retentive dosage forms wherein drug release in the lower gastrointestinal tract and colon is restricted, and the majority of the drug dose is delivered to the stomach and upper gastrointestinal tract. The invention is useful not only in conjunction with the delivery of ciprofloxacin, fluoroquinolone antibacterial agents in general, and other antibiotics, but also with a host of active agents for which restricted delivery in the lower intestinal tract is desirable.

SUMMARY OF THE INVENTION

The present invention is directed to the aforementioned need in the art, and provides a controlled release oral dosage form for the continuous, sustained administration of a pharmacologically active agent to the upper G.I. tract of a patient in whom the fed mode has been induced. The majority of the agent is delivered, on an extended release basis, to the stomach, duodenum and upper regions of the small intestine, with drug delivery in the lower gastrointestinal tract and colon substantially restricted. The dosage form comprises a matrix of a biocompatible, hydrophilic, erodible polymer with an active agent incorporated therein, with the active agent preferably representing at least about 60% by volume the dosage form, wherein the polymer is one that both swells in the

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presence of water and gradually erodes over a time period of hours, with swelling and erosion commencing upon contact with gastric fluid.

In order to deliver the majority of the drug dose to the stomach and upper G.I. tract and avoid or at least minimize delivery of the drug to the lower intestine and colon, the drug release period should be less than that of the sum of the mean gastric emptying time and the transit time through the small intestine. For drugs having low aqueous solubility, this means that the duration of erosion—which is approximately equivalent to the drug release period with such active agents—should be less than that of the sum of the mean gastric emptying time and the transit time through the small intestine. The dosage forms of the invention are particularly adapted for delivery of active agents whose aqueous solubility decreases as pH increases, such as ciprofloxacin and other fluoroquinolone antibiotics, such that any active agent remaining in the dosage form upon passage from the acidic region of the stomach and upper G.I. tract into the much more basic lower G.I. tract will not be in solution, and, therefore, not available for absorption.

Further, in order to minimize variability in the rate of absorption, C_{max} and t_{max} from patient to patient, it is necessary to minimize the variability in the rate of drug release from gastric retentive dosage forms. The ratio of erosion rate “ER” obtained in vitro using a disintegration test (i.e., the rate of drug release as a result of dosage form erosion or disintegration) to the dissolution rate “DR” obtained in vitro using a dissolution test (i.e., the rate of drug release as a result of swelling, dissolution, and diffusion out of the matrix), can be adjusted in the present dosage forms, not only to optimize the site of drug delivery, but also to provide a dosage form wherein the dependency of the release profile on mechanical and hydrodynamic forces is minimized, thereby, in turn, minimizing variability in the rate of drug release. The ratio of the aforementioned ER to DR values obtained in vitro should generally be in the range of about 1.2:1 to 5:1, preferably about 1.2:1 to 3:1, more preferably about 1.3:1 to 2:1, and most preferably about 1.5:1 to 2:1. Optimization of the ER to DR ratio may be controlled by adjusting the size and/or shape of the dosage form, by selecting matrix polymers having particular swelling and erosion rates, by increasing or decreasing drug loading, and by using additives such as disintegrants and solubilizers. For example, the rate of diffusion of dissolved active agent out of the matrix (the DR) can be slowed relative to the rate at which the active agent is released via polymer erosion (the ER) by increasing the volume fraction of drug and selecting a polymer that will erode faster than it will swell.

These dosage forms can minimize or even eliminate problems such as the overgrowth of detrimental intestinal flora resulting from drugs that are toxic to normal intestinal flora, by delivering the bulk of the drug dose to the upper G.I. tract and allowing little or no drug to reach the lower G.I. tract or colon. The dosage forms can also prevent chemical degradation of drugs by intestinal enzymes, as alluded to above, loss of bioavailability of a drug due to its leaving the acidic environment of the stomach, and chemical degradation of a drug in the neutral to alkaline environment of the gastrointestinal tract. Finally, the dosage form can extend the drug delivery period so as to allow less frequent administration. For example, the invention enables preparation of once-a-day dosage forms for the administration of fluoroquinolone antibiotics such as ciprofloxacin, which are currently administered at least twice daily.

When used to administer drugs that are highly soluble in aqueous acid, the active agent may be contained within a

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vesicle that prevents a too rapid release rate in the acidic environment of the upper G.I. tract. Suitable vesicles include, but are not limited to, liposomes and nanoparticles, including nanocrystals, nanospheres and nanocapsules.

In a further embodiment of this invention, the dosage form is a bilayer tablet, a trilayer tablet, or a shell-and-core tablet, with bilayer and trilayer tablets preferred. With the bilayer tablet, one layer contains drug and is comprised of a polymer that is primarily erodible, and a second, swellable layer may contain the same drug, a different drug, or no drug. The function of the swelling layer is to provide sufficient particle size throughout the entire period of drug delivery to promote gastric retention in the fed mode. With the trilayer tablet, the outer layers contain drug and are comprised of a polymer that is primarily erodible, while the middle layer is swellable.

The invention additionally provides a method for using these dosage forms to administer drugs on an extended basis to the stomach, duodenum and upper sections of the small intestine, while minimizing delivery to the lower G.I. tract and colon, as well as a method for preparing the dosage forms so as to achieve the aforementioned targeted delivery profile while minimizing patient-to-patient variability. The latter method involves preparing the dosage form with a predetermined ratio of disintegration release ER to dissolution release DR. The ER may be evaluated using any suitable disintegration test that is predictive of drug release behavior in vivo, although a particularly preferred such test is the standard USP Disintegration Test as set forth in USP 24-NF 19, Supplement 4, Section 701, published by the United States Pharmacopeia & National Formulary in 2001, or a modification of the standard test. The pertinent information obtained using the disintegration test is the “disintegration time,” a term that is used interchangeably herein with the terms “erosion rate,” “erosion release,” “disintegration rate,” and “disintegration release,” and generally refers to the time for complete disintegration of the dosage form to occur, wherein “complete disintegration” is as defined as the state in which less than 10%, preferably less than 5%, of the original dosage form (or the active agent-containing layer in a bilayer or trilayer tablet) remains visible. If the test is stopped prior to complete disintegration, the fraction of the dosage form that has disintegrated is noted along with the time of the monitoring period (for example, the ER may be reported as “40% released at 4 hours,” “80% released at 8 hours,” or the like). The DR, on the other hand, is generally evaluated using USP Dissolution Test equipment and the standard USP Dissolution Test as set forth in USP 24-NF 19, Supplement 4, Section 711, which calls for immersion of a dosage in a specified solvent at 37° C. for a given time period, using either a basket stirring element or a paddle stirring element (respectively referred to as “Apparatus 1” and “Apparatus 2” in USP 24-NF 19). At regular time intervals, a sample of the solvent is withdrawn and the drug concentration therein determined, e.g., by HPLC. The pertinent information obtained using the dissolution test is the “dissolution release,” a term that is used interchangeably herein with the terms “dissolution rate,” “dissolution release,” “swelling rate,” and “diffusion rate,” and refers to the time for complete release of drug to occur, wherein “complete release” is as defined as the state in which greater than 90%, preferably greater than 95% of the drug has been released. As with the ER, if the test is stopped prior to complete release, the fraction of drug released is noted along with the time of the monitoring period.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1 and 2 are plots showing the in vitro release characteristics of the four dosage forms evaluated in Example 1, evaluated using both a disintegration test and a dissolution test.

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FIGS. 3 and 4 are plots showing the difference in absorption in vivo between the four dosage forms evaluated in Example 1.

FIG. 5 is a plot showing the release curves obtained from a single layer matrix formulation, using both a disintegration test and a dissolution test, as described in Example 2.

FIG. 6 is a plot showing the release curves obtained from bilayer and trilayer tablets as described in Example 2.

FIGS. 7 and 8 are plots showing the dissolution and disintegration profiles at pH 1 and 6.8, respectively, obtained in vitro for the gastric retentive dosage forms evaluated in Example 3.

FIG. 9 is a plot of plasma level versus time for an in vivo study carried out with ciprofloxacin HCl dosage forms, as described in Example 4.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Overview:

Before describing the present invention in detail, it is to be understood that this invention is not limited to specific active agents, dosage forms, dosing regimens, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well as two or more different active agents in combination, reference to "a polymer" includes mixtures of two or more polymers as well as a single polymer, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "drug," "active agent," and "pharmacologically active agent" are used interchangeably herein to refer to any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a therapeutic effect in the treatment of a disease or abnormal physiological condition. The terms also encompass pharmaceutically acceptable, pharmacologically active derivatives of those active agents specifically mentioned herein, including, but not limited to, salts, esters, amides, prodrugs, active metabolites, analogs, and the like. When the terms "active agent," "pharmacologically active agent" and "drug" are used, then, or when a particular active agent is specifically identified, it is to be understood that applicants intend to include the active agent per se as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, metabolites, analogs, etc.

The term "dosage form" denotes any form of a pharmaceutical composition that contains an amount of active agent sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with: (1) the characteristics of the particular drug, including both its pharmacological characteristics and its physical characteristics, such as solubility; (2) the characteristics of the swellable matrix, such as its permeability; and (3) the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight

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hours, preferably no more frequently than once every twelve hours, and even more preferably no more frequently than once every twenty-four hours.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, and improvement or remediation of damage. Thus, for example, "treating" a patient involves treating a particular disorder or adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual by inhibiting or causing regression of a disorder or disease.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect.

By "pharmaceutically acceptable," such as in the recitation of a "pharmaceutically acceptable carrier," or a "pharmaceutically acceptable acid addition salt," is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" derivative, refers to a derivative having the same type of pharmacological activity as the parent compound and approximately equivalent in degree. When the term "pharmaceutically acceptable" is used to refer to a derivative (e.g., a salt) of an active agent, it is to be understood that the compound is pharmacologically active as well. When the term, "pharmaceutically acceptable" is used to refer to an excipient, it implies that the excipient has met the required standards of toxicological and manufacturing testing or that it is on the Inactive Ingredient Guide prepared by the FDA.

The term "biocompatible" is used interchangeably with the term "pharmaceutically acceptable."

The term "soluble," as used herein, refers to a drug having an aqueous solubility (measured in water at 20° C.) greater than 10%, preferably greater than 35%, by weight. The terms "slightly soluble" and "sparingly soluble" refer to a drug having an aqueous solubility (measured at 20° C.) in the range of 2% to 10% by weight, while drugs having an aqueous solubility in the range of 0.001% to less than 2% by weight are referred to as "substantially insoluble."

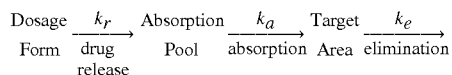
The term "vesicle," as used herein, refers to a small (usually 0.01 to 1.0 mm), usually spherical, membrane-bound structure that may contain or be composed of either lipoidal or aqueous material, or both. Suitable vesicles include, but are not limited to, liposomes, nanoparticles, and microspheres composed of amino acids. While some of these particles, especially nanoparticles and microspheres, need not be membrane-bound structures, for the purposes of the present invention, they are encompassed by the term "vesicle."

The term "controlled release" is intended to refer to any drug-containing formulation in which release of the drug is not immediate, i.e., with a "controlled release" formulation, oral administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "nonimmediate release" as defined in Remington: *The Science and Practice of Pharmacy, Nineteenth Ed.* (Easton, Pa.: Mack Publishing Company, 1995). As discussed

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therein, immediate and nonimmediate release can be defined kinetically by reference to the following equation:



The "absorption pool" represents a solution of the drug administered at a particular absorption site, and k_r , k_a and k_e are first-order rate constants for (1) release of the drug from the formulation, (2) absorption, and (3) elimination, respectively. For immediate release dosage forms, the rate constant for drug release k_r is far greater than the absorption rate constant k_a . For controlled release formulations, the opposite is true, i.e., $k_r \ll k_a$, such that the rate of release of drug from the dosage form is the rate-limiting step in the delivery of the drug to the target area. It should be noted that this simplified model uses a single first order rate constant for release and absorption, and that the controlled release kinetics with any particular dosage form may be much for complicated. In general, however, the term "controlled release" as used herein includes any nonimmediate release formulation.

The term "sustained release" is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period.

The terms "hydrophilic" and "hydrophobic" are generally defined in terms of a partition coefficient P , which is the ratio of the equilibrium concentration of a compound in an organic phase to that in an aqueous phase. A hydrophilic compound has a P value less than 1.0, typically less than about 0.5, where P is the partition coefficient of the compound between octanol and water, while hydrophobic compounds will generally have a P greater than about 1.0, typically greater than about 5.0. The polymeric carriers herein are hydrophilic, and thus compatible with aqueous fluids such as those present in the human body.

The term "polymer" as used herein refers to a molecule containing a plurality of covalently attached monomer units, and includes branched, dendrimeric and star polymers as well as linear polymers. The term also includes both homopolymers and copolymers, e.g., random copolymers, block copolymers and graft copolymers, as well as uncrosslinked polymers and slightly to moderately to substantially crosslinked polymers.

The terms "swellable" and "bioerodible" (or simply "erodible") are used to refer to the polymers used in the present dosage forms, with "swellable" polymers being those that are capable of absorbing water and physically swelling as a result, with the extent to which a polymer can swell being determined by the degree of crosslinking, and "bioerodible" or "erodible" polymers referring to polymers that slowly dissolve and/or gradually hydrolyze in an aqueous fluid, and/or that physically erodes as a result of movement within the stomach or gastrointestinal tract.

The in vivo "release rate" and in vivo "release profile" refer to the time it takes for the orally administered dosage form, or the active agent-containing layer of a bilayer or trilayer tablet (again, administered when the stomach is in the fed mode) to be reduced to 0-10%, preferably 0-5%, of its original size, as may be observed visually using NMR shift reagents or paramagnetic species, radio-opaque species or markers, or radiolabels. Unless otherwise indicated herein, all references to in

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vivo tests and in vivo results refer to results obtained upon oral administration of a dosage form with food, such that the stomach is in the fed mode.

The term "fed mode," as used herein, refers to a state which is typically induced in a patient by the presence of food in the stomach, the food giving rise to two signals, one that is said to stem from stomach distension and the other a chemical signal based on food in the stomach. It has been determined that once the fed mode has been induced, larger particles are retained in the stomach for a longer period of time than smaller particles. Thus, the fed mode is typically induced in a patient by the presence of food in the stomach.

In the normal digestive process, the passage of matter through the stomach is delayed by a physiological condition that is variously referred to as the digestive mode, the postprandial mode, or the "fed mode." Between fed modes, the stomach is in the interdigestive or "fasting" mode. The difference between the two modes lies in the pattern of gastroduodenal motor activity.

In the fasting mode, the stomach exhibits a cyclic activity called the interdigestive migrating motor complex ("IMMC"). This activity occurs in four phases:

Phase I, which lasts 45 to 60 minutes, is the most quiescent, with the stomach experiencing few or no contractions;

Phase II, characterized by sweeping contractions occurring in an irregular intermittent pattern and gradually increasing in magnitude;

Phase III consisting of intense bursts of peristaltic waves in both the stomach and the small bowel, lasting for about 5 to 15 minutes; and

Phase IV is a transition period of decreasing activity which lasts until the next cycle begins.

The total cycle time for all four phases is approximately 90 minutes. The greatest activity occurs in Phase III, when powerful peristaltic waves sweep the swallowed saliva, gastric secretions, food particles, and particulate debris, out of the stomach and into the small intestine and colon. Phase III thus serves as an intestinal housekeeper, preparing the upper tract for the next meal and preventing bacterial overgrowth.

The fed mode is initiated by nutritive materials entering the stomach upon the ingestion of food. Initiation is accompanied by a rapid and profound change in the motor pattern of the upper gastrointestinal tract, over a period of 30 seconds to one minute. The change is observed almost simultaneously at all sites along the G.I. tract and occurs before the stomach contents have reached the distal small intestine. Once the fed mode is established, the stomach generates 3-4 continuous and regular contractions per minute, similar to those of the fasting mode but with about half the amplitude. The pylorus is partially open, causing a sieving effect in which liquids and small particles flow continuously from the stomach into the intestine while indigestible particles greater in size than the pyloric opening are retropelled and retained in the stomach. This sieving effect thus causes the stomach to retain particles exceeding about 1 cm in size for approximately 4 to 6 hours.

Accordingly, the present drug delivery systems are used to administer a drug to the fed stomach and upper G.I. tract while minimizing drug release in the lower G.I. tract and colon. The method is particularly useful in conjunction with the delivery of drugs that are toxic to normal intestinal flora or are used to treat a local condition or disorder, e.g., a stomach ulcer. The dosage forms, having an optimized ratio of erosion rate to dissolution rate and, preferably, although not necessarily, a volume fraction of the drug of at least 60%, provide for effective delivery of drugs to the upper G.I. tract, with delivery to the lower G.I. tract and colon restricted and the drug delivery period in the upper G.I. tract extended relative

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to the delivery period associated with immediate release and prior gastric retentive dosage forms. The dosage forms are particularly suited to administration of drugs whose aqueous solubility decreases with increasing pH, such that the drug is substantially more soluble in the acidic environment of the stomach than in the more basic regions of the lower G.I. tract.

The dosage forms of the invention are comprised of at least one biocompatible, hydrophilic, erodible polymer with a drug dispersed therein. The swelling properties of the polymer(s) are important insofar as they promote gastric retention of the dosage forms in the fed stomach. For drug delivery to the stomach and upper G.I. tract, a polymer is used that (i) swells unrestrained dimensionally via imbibition of gastric fluid to increase the size of the particles to promote gastric retention within the stomach of a patient in whom the fed mode has been induced, (ii) gradually erodes over a time period of hours, with the erosion commencing upon contact with the gastric fluid, and (iii) releases the drug to the stomach, duodenum and upper G.I. tract at a rate that, in general, is primarily dependent on the erosion rate. That is, with respect to the latter requirement, preferred dosage forms have an erosion rate that is slightly faster than the swelling rate, such that drug release from the dosage form is primarily controlled by polymer erosion than by polymer swelling.

II. Optimization Using Disintegration and Dissolution Tests:

The preferred composition of a dosage form of the invention gives rise not only to the desired drug release profile in vivo, i.e., a release profile wherein the majority of the drug dose is delivered to the upper G.I. tract with restricted delivery to the lower G.I. tract, but also effectively minimizes patient-to-patient variability in release profile. One of the ways the invention accomplishes this is by providing a dosage form whose ER to DR is optimized such that the ratio of ER to DR is in the range of about 1.2:1 to 5:1, preferably about 1.2:1 to 3:1, more preferably about 1.3:1 to 2:1, and most preferably about 1.5:1 to 2:1.

The ER may be evaluated using any suitable disintegration test, although a particularly preferred such test is the standard USP Disintegration Test as set forth in USP 24-NF 19, Supplement 4, Section 701, published by the United States Pharmacopeia & National Formulary in 2001, or a modification of the standard test. As explained in the aforementioned section of USP 24-NF 19, the USP Disintegration apparatus consists of a basket-rack assembly, a 1000-ml beaker, 142 to 148 mm in height and having an outside diameter of 103 to 108 mm, a thermostatic arrangement for heating an immersion fluid between 35° C. and 39° C., and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of 5.3 cm to 5.7 cm. The time required for the upward and downward strokes is the same, and the volume of the fluid in the vessel is such that the wire mesh of the basket remains at least 2.5 cm below the fluid surface on the upward stroke, and should not descend to within less than 2.5 cm of the bottom of the vessel on the downward stroke. There should be no appreciable horizontal movement of the basket rack assembly; the assembly moves solely in a vertical direction, along its axis. The basket-rack assembly consists of six open-ended transparent tubes, each having dimensions specified in the aforementioned section of USP 24-NF 19; the tubes are held in a vertical position by two plastic plates, with six holes equidistance from the center of the plate and equally spaced from one another. Attached to the undersurface of the lower plate is a woven stainless steel wire mesh. A suitable means is provided to suspend the basket-rack assembly from a raising and lowering device.

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Accordingly, the USP Disintegration Test is conducted using the above-described test equipment by placing the dosage form to be tested in each basket-rack assembly, immersing the assembly in a specified fluid at a temperature between 35° C. and 39° C. for a given time period, and raising and lowering the basket in the immersion fluid through a distance of about 5.5 cm at a frequency of about 30 cycles per minute. The dosage forms are visually inspected at specified times for complete disintegration. The particularly preferred disintegration test used in conjunction with the invention is a modification of the standard USP Disintegration Test wherein one to three tablets are tested per basket, an extended monitoring time is used, e.g., a four-hour to twenty-four-hour time period, generally a two-hour to twenty-four hour period, preferably a four- to eight-hour time period, and wherein a thin plastic disk (9.5±0.15 mm in thickness, 20.7±0.15 mm in diameter) is placed on each dosage form (noted as optional in Section 701 of USP 24-NF 19).

The DR is evaluated using a dissolution test that is predictive of drug release behavior, with the USP Disintegration Test (as set forth in USP 24-NF 19, Supplement 4, Section 711) or a modification of the standard test. Either of two devices is used in the USP Disintegration Test, "Apparatus 1" and "Apparatus 2." Apparatus 1 consists of a covered vessel, a motor, a metallic drive shaft, and a cylindrical basket that serves a stirring element. The vessel is made of a material that does not sorb, react, or interfere with the dosage forms to be tested, with glass and other inert, transparent materials preferred. The vessel is partially immersed in a water bath or placed in a heating jacket, such that the temperature inside the vessel is maintained at 37±0.5° C. during the test, with the water in the water bath, if used, kept in constant, smooth motion by the rotating basket. A device that allows for observation of the dosage form during the test is preferred. The vessel is cylindrical, with a hemispherical bottom and one of the following dimensions: height of 160 mm to 210 mm, inside diameter of 98 mm to 106 mm, capacity of 1 liter; height of 280 mm to 300 mm, inside diameter of 98 mm to 106 mm, capacity of 2 liters; and height of 280 mm to 300 mm, inside diameter of 145 mm to 155 mm, capacity of 4 liters. The shaft is positioned so that the distance between the shaft axis and the vertical axis of the vessel is less than 2 mm, at all points, thus ensuring smooth rotation without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be controlled.

USP Dissolution Apparatus 2 is similar to that of Apparatus 1, except that the rotating basket is replaced with a paddle formed from a blade and a shaft, with the blade and shaft integrated so as to comprise a single structural entity. The paddle may be metallic (composed of, for example, 303 stainless steel) or it may be comprised of some other suitably inert, rigid material. A distance of 25±2 mm is maintained between the blade and the inside bottom of the vessel, during the test. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material (such as not more than a few turns of a wire helix) may be attached to dosage units that would otherwise float.

The preferred dissolution apparatus used herein is the USP Apparatus 1, using standard 40-mesh rotating baskets, a basket rotation speed of 100 rpm, a 1-liter vessel containing a dissolution medium specified in the individual USP monograph for the particular active agent and type of dosage form being tested (e.g., 900 mL deionized (DI) water for sustained release ciprofloxacin tablets) as the dissolution medium, anti-evaporation covers, and a Distek Dissolution System 2100B USP Bath or equivalent. The dissolution test is carried out by

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assembling the apparatus as described above and as explained in detail in Section 711 of USP 24- NF 19, filling the 1-liter vessels with 900 mL deionized (DI) water as the dissolution medium, and equilibrating the DI water to $37 \pm 0.5^\circ \text{C}$. Each dosage form is weighed and placed in into a dry 40-mesh basket, and then lowered into the DI water at to. Samples are removed as 5.0 mL aliquots at various time points, typically although not necessarily at 1, 2, 4, 6 and 8 hours, from a zone midway between the surface of the DI water and the top of the rotating basket, not less than 1 cm from the vessel wall. Quantitation may then be performed using any suitable technique, with reverse phase liquid chromatography and an ultraviolet detection system.

To optimize the ER-to-DR ratio for a particular drug, various dosage forms can be prepared and evaluated for their ER and DR using the above tests. That is, one or more matrix polymers are selected along with an active agent to be administered, and different dosage forms are prepared using different matrix polymers and/or active agents, matrix polymers of different molecular weights, matrix polymers crosslinked to different degrees, and/or different amounts of different components, such as lubricants, solubilizers, disintegrants, and the like. Those dosage forms that exhibit an optimized ER-to-DR ratio, i.e., in the range of about 1.2:1 to 5:1, preferably about 1.2:1 to 3:1, more preferably about 1.3:1 to 2:1, and most preferably about 1.5:1 to 2:1.

III. Swellable, Bioerodible Polymers:

The polymer used in the dosage forms of the present invention should not release the drug at too rapid a rate so as to result in a drug overdose or rapid passage into and through the upper gastrointestinal tract (i.e., in less than about four hours), nor should the polymer release drug too slowly to achieve the desired biological effect. That is, the majority of the drug dose should be delivered in the stomach and upper G.I. tract, but drug release in the stomach and upper G.I. tract should still occur over an extended time period. Polymers that permit a rate of drug release that achieves the requisite pharmacokinetics for a desired duration, as determined using the USP Dissolution and Disintegration Tests, are selected for use in the dosage forms of the present invention.

Polymers suitable for use in the present invention are those that both swell upon absorption of gastric fluid and gradually erode over a time period of hours. Erosion initiates simultaneously with the swelling process, upon contact of the surface of the dosage form with gastric fluid. Erosion reflects the dissolution of the polymer beyond the polymer gel-solution interface where the polymer has become sufficiently dilute that it can be transported away from the dosage form by diffusion or convection. This may also depend on the hydrodynamic and mechanical forces present in the gastrointestinal tract during the digestive process. While swelling and erosion occur at the same time, it is preferred herein that drug release should be erosion-controlled, meaning that the selected polymer should be such that complete drug release occurs primarily as a result of erosion rather than swelling and dissolution. However, swelling should take place at a rate that is sufficiently fast to allow the tablet to be retained in the fed stomach for a time period in the range of about 2-12 hours, preferably in the range of about 4-9 hours. At minimum, for an erosional gastric retentive dosage form, there should be an extended period during which the dosage form maintains its size before it is diminished by erosion.

Suitable polymers for use in the present dosage forms may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, if copoly-

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mers, either random copolymers, block copolymers or graft copolymers. Synthetic hydrophilic polymers useful herein include, but are not limited to:

- polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers;
- cellulosic polymers;
- acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate;
- maleic anhydride copolymers;
- polymaleic acid;
- poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide);
- poly(olefinic alcohol)s such as poly(vinyl alcohol);
- poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof;
- polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol;
- polyoxyethylated sorbitol and polyoxyethylated glucose;
- polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline);
- polyvinylamines;
- polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like;
- polyimines, such as polyethyleneimine;
- starch and starch-based polymers;
- polyurethane hydrogels;
- chitosan;
- polysaccharide gums;
- zein; and
- shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate.

The term "cellulosic polymer" is used herein to denote a linear polymer of anhydroglucose. Cellulosic polymers that can be used advantageously in the present dosage forms include, without limitation, hydroxymethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropylcellulose phthalate, cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, carboxymethylcellulose, carboxymethylcellulose sodium, and microcrystalline cellulose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the GI tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 50 to about 110,000 centipoise as a 2% aqueous solution at 20°C . Another class includes those whose viscosity is within the range of about 800 to about 6,000 centipoise as a 1% aqueous solution at 20°C . Particularly preferred alkyl-substituted cel-

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luloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A presently preferred hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

Polyalkylene oxides are the preferred polymers herein, and the polyalkylene oxides that are of greatest utility are those having the properties described above for alkyl-substituted cellulose polymers. A particularly preferred polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For purposes of this invention, a preferred viscosity range is about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20° C. Preferred poly(ethylene oxide)s are Polyox® 303, Polyox® Coag, Polyox® 301, Polyox® WSR N-60K, Polyox® WSR 1105 and Polyox® WSR N-80, having number average molecular weights of 7 million, 5 million, 4 million, 2 million, 900,000 and 200,000, respectively, all products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamnan gum. Xanthan gum is preferred.

Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Preferred crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25° C. Three presently preferred examples are CARBOPOL® NF grades 971P, 974P and 934P (BF Goodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples are polymers known as WATER LOCK®, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

Suitable polymers also include naturally occurring hydrophilic polymers such as, by way of example, proteins such as collagen, fibronectin, albumins, globulins, fibrinogen, fibrin and thrombin; aminated polysaccharides, particularly the glycosaminoglycans, e.g., hyaluronic acid, chitin, chondroitin sulfate A, B, or C, keratin sulfate, keratosulfate and heparin; guar gum; xanthan gum; carageenan; alginates; pectin; and activated polysaccharides such as dextran and starches.

The aforementioned list of polymers is not exhaustive, and a variety of other synthetic hydrophilic polymers may be used, as will be appreciated by those skilled in the art.

The polymer may include biodegradable segments and blocks, either distributed throughout the polymer's molecular structure or present as a single block, as in a block copolymer. Biodegradable segments are those that degrade so as to break covalent bonds. Typically, biodegradable segments are segments that are hydrolyzed in the presence of water. Biodegradable segments may be composed of small molecular segments such as ester linkages, anhydride linkages, ortho ester linkages, ortho carbonate linkages, amide linkages, phosphonate linkages, etc.

Any polymer or polymers of the matrix may also be crosslinked, with the degree of crosslinking directly affecting the rate of polymer swelling as well as the erosion rate. That is, a polymer having a higher degree of crosslinking will exhibit less swelling and slower erosion than a polymer having a lower degree of crosslinking. Crosslinked polymers may be prepared using the above-mentioned exemplary polymers using conventional crosslinking procedures (e.g., chemical crosslinking with an added crosslinking agent, pho-

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tolytically induced crosslinking, etc.), or the polymers may be obtained commercially in crosslinked form.

The water-swellaable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples include, but are not limited to, the following: a cellulosic polymer combined with a gum, such as hydroxyethylcellulose or hydroxypropylcellulose combined with xanthan gum; a polyalkylene oxide combined with a gum, such as poly(ethylene oxide) combined with xanthan gum; and a polyalkylene oxide combined with a cellulosic polymer, such as poly(ethylene oxide) combined with hydroxyethylcellulose, hydroxypropylcellulose, and/or hydroxypropyl methylcellulose.

Combinations of different poly(ethylene oxide)s are also contemplated, with polymers of different molecular weights contributing to different dosage form characteristics. For example, a very high molecular weight poly(ethylene oxide) such as Polyox® 303 (with a number average molecular weight of 7 million) or Polyox® Coag (with a number average molecular weight of 5 million) may be used to significantly enhance diffusion relative to disintegration release by providing high swelling as well as tablet integrity. Incorporating a lower molecular weight poly(ethylene oxide) such as Polyox® WSR N-60K (number average molecular weight approximately 2 million) with Polyox® 303 and/or Polyox® Coag increases disintegration rate relative to diffusion rate, as the lower molecular weight polymer reduces swelling and acts as an effective tablet disintegrant. Incorporating an even lower molecular weight poly(ethylene oxide) such as Polyox® WSR N-80 (number average molecular weight approximately 200,000) further increases disintegration rate.

The hydrophilicity and water swellability of the polymers used herein cause the drug-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of a drug from the matrix is primarily dependent upon the rate of water imbibition and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn is related to the solubility and dissolution rate of the drug, the drug particle size and the drug concentration in the matrix.

The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. Preferably, the amount of polymer is effective to provide a desired extended release period within the fed stomach, such that the time to reach maximum plasma concentration (t_{max}) is at least one hour longer, preferably at least two hours longer, and most preferably at least three hours longer, than that observed with immediate release dosage forms intended to deliver the same drug. In this way, the required doses per day can be reduced. However, a competing consideration is the desirability of releasing the majority of drug in the stomach and upper G.I. tract, meaning that the amount of polymer should also be effective to release most of or even all the drug before the drug and/or dosage form passes into the lower intestinal tract. Ideally, at least 75 wt. %, preferably at least 85 wt. %, and more preferably at least 90 wt. % of the drug is released to the stomach, duodenum, and upper intestinal tract within two to ten hours, preferably within four to nine hours, more preferably within four to six hours, after ingestion. Both goals here can be easily attained with active agents such as ciprofloxacin that exhibit their

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therapeutic effect for a time period extending beyond their half-life, meaning that only a modest extension of the drug delivery period is necessary to reduce the number of doses per day, e.g., from a twice-a-day dosing regimen to a once-a-day dosing regimen.

It has now been found that higher molecular weight polymers are preferred to provide a desired extended release profile using the present dosage forms. Suitable molecular weights are generally in the range of about 5,000 to about 20,000,000. For sparingly soluble drugs, the polymers have molecular weights preferably in the range of about 5,000 to about 8,000,000, more preferably in the range of about 10,000 to about 5,000,000. For water-soluble drugs, the polymers preferably have molecular weights of at least about 10,000, but the molecular weight used will vary with the selected polymer. For example, for hydroxypropyl methylcellulose, the minimum molecular weight may be as low as 10,000, while for poly(ethylene oxide)s the molecular weight may be far higher, on the order of 2,000,000 or more.

IV. Active Agents:

The dosage forms of the present invention are effective for the continuous, controlled administration of drugs that are capable of acting either locally within the gastrointestinal tract, or systemically by absorption into circulation via the gastrointestinal mucosa. Gastric-retentive dosage forms such as those disclosed and claimed herein are particularly useful for the delivery of drugs that are relatively insoluble, are ionized within the gastrointestinal tract, or require active transport.

Preferred active agents for administration using the present dosage forms are those that have increased aqueous solubility in more acidic media, i.e., those whose aqueous solubility increases with decreasing pH. For example, a relatively hydrophobic basic drug that exists in the form of a free base at about neutral pH but which is ionized at a lower pH could be expected to exhibit the aforementioned solubility profile. The aqueous solubility of the active agent in an acidic environment is not necessarily high; the active agent may in fact be only slightly soluble at low pH, so long as it becomes even less soluble, and preferably substantially insoluble, in water at higher pH. The active agents may be acidic, basic, or in the form of an acid addition salt. Generally, the pH at which the drug becomes substantially insoluble is in the range of 5 to 8, generally 5 to 7.5.

The active agent administered may be any compound that is suitable for oral drug administration; examples of the various classes of active agents that can be administered using the present dosage forms include, but are not limited to: analgesic agents; anesthetic agents; antiarthritic agents; respiratory drugs; anticancer agents; anticholinergics; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihelminthics; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents such as antibiotics and antiviral agents; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastic agents; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; antitubercular agents; antiulcer agents and other gastrointestinal active agents; antiviral agents; anxiolytics; appetite suppressants; attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) drugs; cardiovascular preparations including calcium channel blockers, CNS agents, and vasodilators; beta-blockers and antiarrhythmic agents; central nervous system stimulants; cough and cold preparations, including decongestants; diuretics; genetic materials; herbal remedies; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; leukotriene inhibitors; mitotic inhibitors; muscle

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relaxants; narcotic antagonists; nutritional agents, such as vitamins, essential amino acids and fatty acids; parasympatholytics; peptide drugs; psychostimulants; sedatives; steroids; sympathomimetics; and tranquilizers.

Commonly known drugs that are substantially insoluble or only slightly soluble in water include, by way of example, the following:

Gastrointestinally active agents. Gastrointestinally active agents are particularly preferred drugs that can be administered using the present dosage forms. These types of drugs include agents for inhibiting gastric acid secretion, such as the H_2 receptor antagonists cimetidine, ranitidine, famotidine, and nizatidine, the H^+ , K^+ -ATPase inhibitors (also referred to as "proton pump inhibitors") omeprazole and lansoprazole, and antacids such as calcium carbonate, aluminum hydroxide, and magnesium hydroxide. Also included within this general group are agents for treating infection with *Helicobacter pylori* (*H. pylori*), such as metronidazole, tinidazole, amoxicillin, clarithromycin, tetracycline, thiamphenicol, and bismuth compounds (e.g., bismuth subcitrate and bismuth subsalicylate). Other gastrointestinally active agents administrable using the present dosage forms include, but are not limited to, pentagastrin, carbenoxolone, sulfated polysaccharides such as sucralfate, prostaglandins such as misoprostol, and muscarinic antagonists such as pirenzepine and telenzepine. Additionally included are antidiarrheal agents, antiemetic agents and prokinetic agents such as ondansetron, granisetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, trifluoromazine, domperidone, trimethobenzamide, cisapride, motilin, loperamide, diphenoxylate, and octreotide.

Anti-microbial agents. These include: quinolone antibiotics such as nalidixic acid, and particularly fluorinated quinolone antibiotics such as ciprofloxacin, cinafloxacin, enoxacin, gatifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, sparfloxacin, and trovafloxacin; tetracycline antibiotics and related compounds (chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline, minocycline, rolitetracycline); macrolide antibiotics such as erythromycin, clarithromycin, and azithromycin; streptogramin antibiotics such as quinupristin and dalbapristin; beta-lactam antibiotics, including penicillins (e.g., penicillin G, penicillin VK), antistaphylococcal penicillins (e.g., cloxacillin, dicloxacillin, nafcillin, and oxacillin), extended spectrum penicillins (e.g., aminopenicillins such as ampicillin and amoxicillin, and the antipseudomonal penicillins such as carbenicillin), and cephalosporins (e.g., cefadroxil, cefepime, cephalexin, cefazolin, cefoxitin, cefotetan, cefuroxime, cefotaxime, ceftazidime, and ceftriaxone), and carbapenems such as imipenem, meropenem and aztreonam; aminoglycoside antibiotics such as streptomycin, gentamicin, tobramycin, amikacin, and neomycin; glycopeptide antibiotics such as teicoplanin; sulfonamide antibiotics such as sulfacetamide, sulfabenzamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethazine, sulfamethizole, and sulfamethoxazole; anti-mycobacterials such as isoniazid, rifampin, rifabutin, ethambutol, pyrazinamide, ethionamide, aminosalicylic, and cycloserine; systemic antifungal agents such as itraconazole, ketoconazole, fluconazole, and amphotericin B; antiviral agents such as acyclovir, famciclovir, ganciclovir, idoxuridine, sorivudine, trifluridine, valacyclovir, vidarabine, didanosine, stavudine, zalcitabine, zidovudine, amantadine, interferon alpha, ribavirin and rimantadine; and miscellaneous antimicrobial agents such as chloramphenicol, spectinomycin, polymyxin B (colistin), bacitracin, nitrofurantoin, methenamine mandelate and methenamine hippurate.

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Anti-diabetic agents. These include, by way of example, acetohexamide, chlorpropamide, ciglitazone, gliclazide, glipizide, glucagon, glyburide, miglitol, pioglitazone, tolazamide, tolbutamide, triamterine, and troglitazone.

Analgesics. Non-opioid analgesic agents include apazone, etodolac, difenpiramide, indomethacin, meclofenamate, mefenamic acid, oxaprozin, phenylbutazone, piroxicam, and tolmetin; opioid analgesics include alfentanil, buprenorphine, butorphanol, codeine, drocode, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propoxyphene, sufentanil, and tramadol.

Anti-inflammatory agents. Anti-inflammatory agents include the nonsteroidal anti-inflammatory agents, e.g., the propionic acid derivatives as ketoprofen, flurbiprofen, ibuprofen, naproxen, fenoprofen, benoxaprofen, indoprofen, pirofen, carprofen, oxaprozin, pranoprofen, suprofen, alminoprofen, butibufen, and fenbufen; apazone; diclofenac; difenpiramide; diflunisal; etodolac; indomethacin; ketorolac; meclofenamate; nabumetone; phenylbutazone; piroxicam; sulindac; and tolmetin. Steroidal anti-inflammatory agents include hydrocortisone, hydrocortisone-21-monoesters (e.g., hydrocortisone-21-acetate, hydrocortisone-21-butyrate, hydrocortisone-21-propionate, hydrocortisone-21-valerate, etc.), hydrocortisone-17,21-diester (e.g., hydrocortisone-17,21-diacetate, hydrocortisone-17-acetate-21-butyrate, hydrocortisone-17,21-dibutyrate, etc.), alclometasone, dexamethasone, flumethasone, prednisolone, and methylprednisolone.

Anti-convulsant agents. Suitable anti-convulsant (anti-seizure) drugs include, by way of example, azetazolamide, carbamazepine, clonazepam, clorazepate, ethosuximide, ethotoin, felbamate, lamotrigine, mephentoin, mephobarbital, phenytoin, phenobarbital, primidone, trimethadione, vigabatrin, topiramate, and the benzodiazepines. Benzodiazepines, as is well known, are useful for a number of indications, including anxiety, insomnia, and nausea.

CNS and respiratory stimulants. CNS and respiratory stimulants also encompass a number of active agents. These stimulants include, but are not limited to, the following: xanthines such as caffeine and theophylline; amphetamines such as amphetamine, benzphetamine hydrochloride, dextroamphetamine, dextroamphetamine sulfate, levamphetamine, levamphetamine hydrochloride, methamphetamine, and methamphetamine hydrochloride; and miscellaneous stimulants such as methylphenidate, methylphenidate hydrochloride, modafinil, pemoline, sibutramine, and sibutramine hydrochloride.

Neuroleptic agents. Neuroleptic drugs include antidepressant drugs, antimanic drugs, and antipsychotic agents, wherein antidepressant drugs include (a) the tricyclic antidepressants such as amoxapine, amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine, (b) the serotonin reuptake inhibitors citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine, (c) monoamine oxidase inhibitors such as phenelzine, tranlycypromine, and (-)-selegiline, and (d) other, "atypical" antidepressants such as nefazodone, trazodone and venlafaxine, and wherein antimanic and antipsychotic agents include (a) phenothiazines such as acetophenazine, acetophenazine maleate, chlorpromazine, chlorpromazine hydrochloride, fluphenazine, fluphenazine hydrochloride, fluphenazine enanthate, fluphenazine decanoate, mesoridazine, mesoridazine besylate, perphenazine, thioridazine, thioridazine hydrochloride, trifluoperazine, and trifluoperazine hydrochloride, (b) thioxanthenes such as chlorprothixene, thiothixene, and thiothixene hydro-

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chloride, and (c) other heterocyclic drugs such as carbamazepine, clozapine, droperidol, haloperidol, haloperidol decanoate, loxapine succinate, molindone, molindone hydrochloride, olanzapine, pimozide, quetiapine, risperidone, and sertindole.

Hypnotic agents and sedatives include clomethiazole, ethinamate, etomidate, glutethimide, meprobamate, methypyrrolon, zolpidem, and barbiturates (e.g., amobarbital, propobarbital, butobarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, thiopental).

Anxiolytics and tranquilizers include benzodiazepines (e.g., alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, triazolam), buspirone, chlordiazepoxide, and droperidol.

Anticancer agents, including antineoplastic agents: Paclitaxel, docetaxel, camptothecin and its analogues and derivatives (e.g., 9-aminocamptothecin, 9-nitrocamptothecin, 10-hydroxy-camptothecin, irinotecan, topotecan, 20-O- β -glucopyranosyl camptothecin), taxanes (baccatins, cephalomannine and their derivatives), carboplatin, cisplatin, interferon- α_{2A} , interferon- α_{2B} , interferon- α_{N3} and other agents of the interferon family, levamisole, altretamine, cladribine, tretinoin, procarbazine, dacarbazine, gemcitabine, mitotane, asparaginase, porfimer, mesna, amifostine, mitotic inhibitors including podophyllotoxin derivatives such as teniposide and etoposide and vinca alkaloids such as vinorelbine, vincristine and vinblastine.

Antihyperlipidemic agents. Lipid-lowering agents, or "hyperlipidemic" agents, include HMG-CoA reductase inhibitors such as atorvastatin, simvastatin, pravastatin, lovastatin and cerivastatin, and other lipid-lowering agents such as clofibrate, fenofibrate, gemfibrozil and tacinine.

Anti-hypertensive agents. These include amlodipine, benazepril, darodipine, diltiazem, diazoxide, doxazosin, enalapril, eprosartan, losartan, valsartan, felodipine, fenoldopam, fosinopril, guanabenz, guanadrel, guanethidine, guanfacine, hydralazine, metyrosine, minoxidil, nicardipine, nifedipine, nisoldipine, phenoxymethylamine, prazosin, quinapril, reserpine, and terazosin.

Cardiovascular preparations. Cardiovascular preparations include, by way of example, angiotensin converting enzyme (ACE) inhibitors such as enalapril, 1-carboxymethyl-3-1-carboxy-3-phenyl-(1S)-propylamino-2,3,4,5-tetrahydro-1H-(3S)-1-benzazepine-2-one, 3-(5-amino-1-carboxy-1S-pentyl) amino-2,3,4,5-tetrahydro-2-oxo-3S-1H-1-benzazepine-1-acetic acid or 3-(1-ethoxycarbonyl-3-phenyl-(1S)-propylamino)-2,3,4,5-tetrahydro-2-oxo-(3S)-benzazepine-1-acetic acid monohydrochloride; cardiac glycosides such as digoxin and digitoxin; inotropes such as amrinone and milrinone; calcium channel blockers such as verapamil, nifedipine, nicardipene, felodipine, isradipine, nimodipine, bepridil, amlodipine and diltiazem; beta-blockers such as atenolol, metoprolol; pindolol, propafenone, propranolol, esmolol, sotalol, timolol, and acebutolol; antiarrhythmics such as moricizine, ibutilide, procainamide, quinidine, disopyramide, lidocaine, phenytoin, tocainide, mexiletine, flecainide, encainide, bretylium and amiodarone; and cardioprotective agents such as dexrazoxane and leucovorin; and vasodilators such as nitroglycerin; and diuretic agents such as hydrochlorothiazide, furosemide, bumetanide, ethacrynic acid, torsemide, azosemide, muzolimine, piretanide, and tri-pamide.

Anti-viral agents. Antiviral agents that can be delivered using the present dosage forms include the antiherpes agents

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acyclovir, famciclovir, foscarnet, ganciclovir, idoxuridine, sorivudine, trifluridine, valacyclovir, and vidarabine; the anti-retroviral agents didanosine, stavudine, zalcitabine, and zidovudine; and other antiviral agents such as amantadine, interferon alpha, ribavirin and rimantadine.

Sex steroids. The sex steroids include, first of all, progestogens such as acetoxyprogesterone, allylestrenol, anagestone acetate, chlormadinone acetate, cyproterone, cyproterone acetate, desogestrel, dihydrogesterone, dimethisterone, ethisterone (17 α -ethinyltestosterone), ethynodiol diacetate, flurogestone acetate, gestadene, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxymethylprogesterone, hydroxymethylprogesterone acetate, 3-ketodesogestrel, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol acetate, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, normethisterone, and progesterone. Also included within this general class are estrogens, e.g.: estradiol (i.e., 1,3,5-estratriene-3,17 β -diol, or "17 β -estradiol") and its esters, including estradiol benzoate, valerate, cypionate, heptanoate, decanoate, acetate and diacetate; 17 α -estradiol; ethinylestradiol (i.e., 17 α -ethinylestradiol) and esters and ethers thereof, including ethinylestradiol 3-acetate and ethinylestradiol 3-benzoate; estriol and estriol succinate; polyestrol phosphate; estrone and its esters and derivatives, including estrone acetate, estrone sulfate, and piperazine estrone sulfate; quinestrol; mestranol; and conjugated equine estrogens. Androgenic agents, also included within the general class of sex steroids, are drugs such as the naturally occurring androgens androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androstenediol, androstenediol-3-acetate, androstenediol-17-acetate, androstenediol-3, 17-diacetate, androstenediol-17-benzoate, androstenediol-3-acetate-17-benzoate, androstenedione, dehydroepiandrosterone (DHEA; also termed "prasterone"), sodium dehydroepiandrosterone sulfate, 4-dihydrotestosterone (DHT; also termed "stanolone"), 5 α -dihydrotestosterone, dromostanolone, dromostanolone propionate, ethylestrenol, nandrolone phenpropionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone cyclohexanepropionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, oxandrolone, stanozolol and testosterone; pharmaceutically acceptable esters of testosterone and 4-dihydrotestosterone, typically esters formed from the hydroxyl group present at the C-17 position, including, but not limited to, the enanthate, propionate, cypionate, phenylacetate, acetate, isobutyrate, bucylate, heptanoate, decanoate, undecanoate, caprate and isocaprate esters; and pharmaceutically acceptable derivatives of testosterone such as methyl testosterone, testolactone, oxymetholone and fluoxymesterone.

Muscarinic receptor agonists and antagonists. Muscarinic receptor agonists include, by way of example: choline esters such as acetylcholine, methacholine, carbachol, bethanechol (carbamylmethylcholine), bethanechol chloride, cholinomimetic natural alkaloids and synthetic analogs thereof, including pilocarpine, muscarine, McN-A-343, and oxotremorine. Muscarinic receptor antagonists are generally belladonna alkaloids or semisynthetic or synthetic analogs thereof, such as atropine, scopolamine, homatropine, homatropine methyl bromide, ipratropium, methantheline, methscopolamine and tiotropium.

Peptide drugs. Peptidyl drugs include the peptidyl hormones activin, amylin, angiotensin, atrial natriuretic peptide (ANP), calcitonin, calcitonin gene-related peptide, calcitonin

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N-terminal flanking peptide, ciliary neurotrophic factor (CNTF), corticotropin (adrenocorticotropin hormone, ACTH), corticotropin-releasing factor (CRF or CRH), epidermal growth factor (EGF), follicle-stimulating hormone (FSH), gastrin, gastrin inhibitory peptide (GIP), gastrin-releasing peptide, gonadotropin-releasing factor (GnRF or GNRH), growth hormone releasing factor (GRF, GRH), human chorionic gonadotropin (hCH), inhibin A, inhibin B, insulin, luteinizing hormone (LH), luteinizing hormone-releasing hormone (LHRH), α -melanocyte-stimulating hormone, β -melanocyte-stimulating hormone, γ -melanocyte-stimulating hormone, melatonin, motilin, oxytocin (pitocin), pancreatic polypeptide, parathyroid hormone (PTH), placental lactogen, prolactin (PRL), prolactin-release inhibiting factor (PIF), prolactin-releasing factor (PRF), secretin, somatotropin (growth hormone, GH), somatostatin (SIF, growth hormone-release inhibiting factor, GIF), thyrotropin (thyroid-stimulating hormone, TSH), thyrotropin-releasing factor (TRH or TRF), thyroxine, vasoactive intestinal peptide (VIP), and vasopressin. Other peptidyl drugs are the cytokines, e.g., colony stimulating factor 4, heparin binding neurotrophic factor (HBNF), interferon- α , interferon α -2a, interferon α -2b, interferon α -n3, interferon- β , etc., interleukin-1, interleukin-2, interleukin-3, interleukin-4, interleukin-5, interleukin-6, etc., tumor necrosis factor, tumor necrosis factor- α , granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor, midkine (MD), and thymopoietin. Still other peptidyl drugs that can be advantageously delivered using the present systems include endorphins (e.g., dermorphin, dynorphin, α -endorphin, β -endorphin, γ -endorphin, σ -endorphin, [Leu⁵]enkephalin, [Met⁵]enkephalin, substance P), kinins (e.g., bradykinin, potentiator B, bradykinin potentiator C, kallidin), LHRH analogues (e.g., buserelin, deslorelin, fertirelin, goserelin, histrelin, leuprolide, lutrelin, nafarelin, tryptorelin), and the coagulation factors, such as α_1 -antitrypsin, α_2 -macroglobulin, antithrombin III, factor I (fibrinogen), factor II (prothrombin), factor III (tissue prothrombin), factor V (proaccelerin), factor VII (proconvertin), factor VIII (antihemophilic globulin or AHG), factor IX (Christmas factor, plasma thromboplastin component or PTC), factor X (Stuart-Power factor), factor XI (plasma thromboplastin antecedent or PTA), factor XII (Hageman factor), heparin cofactor II, kallikrein, plasmin, plasminogen, prekallikrein, protein C, protein S, and thrombomodulin and combinations thereof.

Genetic material may also be delivered using the present dosage forms, e.g., nucleic acids, RNA, DNA, recombinant RNA, recombinant DNA, antisense RNA, antisense DNA, ribozymes, ribooligonucleotides, deoxyribonucleotides, antisense ribooligonucleotides, and antisense deoxyribooligonucleotides. Representative genes include those encoding for vascular endothelial growth factor, fibroblast growth factor, Bcl-2, cystic fibrosis transmembrane regulator, nerve growth factor, human growth factor, erythropoietin, tumor necrosis factor, and interleukin-2, as well as histocompatibility genes such as HLA-B7.

In contrast to many erodible dosage forms, the low variability of the present dosage forms is particularly important for poorly soluble drugs such as phenytoin and carbamazepine, both anticonvulsant drugs used in the treatment of epilepsy, as noted above, and for which, due to wide variation in drug absorption from patient to patient, doctors must now titrate their patients individually to find a proper (i.e., safe and effective) dosage regimen. In this regard, the dosage forms of the invention are useful for more consistent delivery of spar-

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ingly soluble drugs that have a narrow therapeutic index, i.e., drugs for which the toxic dose is not significantly higher than the effective dose.

The dosage forms of the present invention are particularly useful for delivering drugs directly into the stomach for an extended period of time, for example, when the drug is preferentially absorbed in the small intestine (e.g., ciprofloxacin), or for providing continuous, local-only (non-systemic) action, for example, when the drug is calcium carbonate, and which when incorporated into the dosage forms of the present invention becomes a non-systemic, controlled-release antacid. The dosage forms are also useful for delivering drugs continuously to the stomach that are only soluble in that portion of the gastrointestinal tract. For instance, the dosage forms of the present invention are useful for the delivery of calcium carbonate or other calcium salts intended to be used as an antacid or as a dietary supplement to prevent osteoporosis. Calcium salts are soluble in the stomach but not in the remainder of the G.I. tract, as a result of the presence of stomach acid. With conventional dosage forms, the dwell time of the delivered agent in the stomach is limited usually to only about 20 to 40 minutes, which, in turn, results in a calcium availability of only about 15 to 30%. As a consequence, extremely large dosage forms (2.5 grams), which are difficult for patients to swallow, are commonly utilized. In contrast, by providing controlled delivery for about 4 to 9 hours, plus gastric retention of from about 2 to 12, preferably 4 to 9 hours, most preferably about 4 to 6 hours, the dosage forms of the present invention assure more complete bioavailability of elemental calcium from the administered drug, i.e., calcium carbonate. This results in a greater likelihood of patients receiving the intended dose and, also, avoids the need for impractically large dosage forms.

The dosage forms of the present invention are also useful for delivering drugs to treat local disorders of the stomach, such as those that are effective for eradicating *Helicobacter pylori* (*H. pylori*) from the submucosal tissue of the stomach, to treat stomach and duodenal ulcers, to treat gastritis and esophagitis and to reduce risk of gastric carcinoma. The dosage forms of the present invention are particularly useful for the foregoing indications because they provide enhanced gastric retention and prolonged release. In a preferred such embodiment, a dosage form of the invention will comprise a combination of (a) bismuth (e.g., as bismuth subsalicylate), (b) an antibiotic such as tetracycline, amoxicillin, thiamphenicol, or clarithromycin, and (c) a proton pump inhibitor, such as omeprazole. A combination of bismuth subsalicylate, thiamphenicol and omeprazole is a particularly preferred combination that may be delivered using the dosage forms of the present invention for the eradication of *H. pylori*.

Drugs delivered from the gastric-retentive, controlled delivery dosage forms of the invention continuously bathe the stomach and upper part of the small intestine—in particular, the duodenum—for many hours. These sites, particularly the upper region of the small intestine, are the sites of most efficient absorption for many drugs. By continually supplying the drug to its most efficient site of absorption, the dosage forms of the present invention allow for more effective oral use of many drugs.

Since the dosage forms of the present invention provide the drug by means of a continuous delivery instead of the pulse-entry delivery associated with conventional dosage forms, two particularly significant benefits result from their use: (1) a reduction in side effects from the drug(s); and (2) an ability to effect treatment with less frequent administration of the drug(s) being used. For instance, when administered in a conventional dosage form, the sparingly soluble drug, cipro-

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floxacin, an antibiotic administered to treat bacterial infections such as urinary tract infections, is currently given two times daily and may be frequently accompanied by gastrointestinal side effects such as diarrhea. However, using the dosage forms of the present invention, the number of daily doses can be decreased to one with a lower incidence of side effects.

The invention is not, however, limited to dosage forms for delivering poorly soluble drugs. Drugs having moderate to substantial aqueous solubility can also be delivered using the present dosage forms. If necessary, they may be encased in a protective vesicle or coated with a protective coating so as to prevent a too rapid release. Preferred such drugs include, without limitation, metformin hydrochloride, vancomycin hydrochloride, captopril, enalapril or its salts, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, doxifluridine, gabapentin, tramadol, fluoxetine hydrochloride, acyclovir, levodopa, ganciclovir, bupropion, lisinopril, losartan, and esters of ampicillin. Particularly preferred such drugs are metformin hydrochloride, gabapentin, lisinopril, enalapril, losartan, and sertraline hydrochloride.

Any of the aforementioned active agents may also be administered in combination using the present dosage forms. Examples of particularly important drug combination products include, but are not limited to, an ACE inhibitor or an angiotensin II antagonist in combination with a diuretic. Specific examples of ACE inhibitors are captopril, lisinopril, or enalapril, and examples of diuretics include triamterene, furosemide, bumetanide, and hydrochlorothiazide. Alternatively, either of these diuretics can advantageously be used in combination with a beta-adrenergic blocking agent such as propranolol, timolol or metoprolol. These particular combinations are useful in cardiovascular medicine, and provide advantages of reduced cost over separate administrations of the different drugs, plus the particular advantage of reduced side effects and enhanced patient compliance. For example, it has been shown that small doses of a diuretic plus small doses of either an ACE inhibitor or a beta blocker provide the additive effects of lowering blood pressure without the additive side effects of the two together.

Particularly preferred drugs for administration using the present dosage forms include, but are not limited to, furosemide, gabapentin, losartan, budesonide, and the antibiotics ciprofloxacin and minocycline. The drugs may be in the form of salts, esters or other derivatives. For example, ciprofloxacin and minocycline may be incorporated as acid addition salts, such as ciprofloxacin hydrochloride and minocycline hydrochloride, respectively.

Drug loading may be expressed in terms of the volume fraction of drug relative to the entire dosage form, or, if the dosage form is a bilayer or trilayer tablet, in terms of the volume fraction of drug relative to the erodible layer in which it is contained. The drug loading in the present dosage forms is in the range of about 0.01% to 80%, but is preferably relatively high, i.e., at least about 60%, preferably in the range of about 60% to 80%.

V. Dosage Forms, Protective Vesicles and Coatings:

The formulations of this invention are typically in the form of matrix/active agent tablets, or matrix/active agent particles compressed into tablets. Other formulations contain matrix/active agent particles in capsules. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and

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described in the pertinent texts, e.g., in Remington, cited supra. Tablets and capsules represent the most convenient oral dosage forms, in which cases solid pharmaceutical carriers are employed.

Tablets may be manufactured using standard tablet processing procedures and equipment. One method for forming tablets is by direct compression of a particulate composition, with the individual particles of the composition comprised of a matrix of a biocompatible, hydrophilic, erodible polymer having the active agent incorporated therein, alone or in combination with one or more carriers, additives, or the like. As an alternative to direct compression, tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist or otherwise tractable material, and using injection or compression molding techniques using suitable molds fitted to a compression unit. Tablets may also be prepared by extrusion in the form of a paste, into a mold, or to provide an extrudate to be "cut" into tablets. However, compression and granulation techniques are preferred, with direct compression particularly preferred.

Tablets prepared for oral administration according to the invention, and manufactured using direct compression, will generally contain other materials such as binders, lubricants, disintegrants, fillers, stabilizers, solubilizers, emulsifiers, surfactants, complexing agents, coloring agents, and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, microcrystalline cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Lubricants are used to facilitate tablet manufacture, promoting powder flow and preventing particle capping (i.e., particle breakage) when pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight, preferably from about 1.5% to 2.5% by weight), calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably less than about 2% by weight). Disintegrants are used to facilitate disintegration of the tablet, thereby increasing the erosion rate relative to the dissolution rate, and are generally starches, clays, celluloses, algin, gums, or crosslinked polymers (e.g., crosslinked polyvinyl pyrrolidone). Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, and sorbitol. Solubility-enhancers, including solubilizers per se, emulsifiers, and complexing agents (e.g., cyclodextrins), may also be advantageously included in the present formulations. Stabilizers, as well known in the art, are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions.

As noted above, the active agent/polymer matrix particles of the invention may also be administered in packed capsules. Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: *The Science and Practice of Pharmacy*, cited supra, which describes materials and methods for preparing encapsulated pharmaceuticals.

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As previously mentioned, the dosage forms of the present invention can additionally be used to deliver a drug incorporated into a protective vesicle and/or coated with a protective coating. That is, as explained in U.S. Pat. No. 5,972,389 to Shell et al., cited supra, water-soluble drugs can be rendered substantially insoluble or only slightly soluble when incorporated into protective vesicles and/or coated with a protective coating. Suitable vesicles include, but are not limited to, liposomes and nanoparticles, e.g., nanospheres, nanocapsules and nanocrystals composed of amino acids. Vesicles may also be used to solubilize drugs that otherwise have limited aqueous solubility.

By incorporating a drug either in a protective vesicle or protective coating into the dosage form of the present invention, the benefits of gastric retention and gradual release to the upper G.I. tract are combined with the advantageous properties of the vesicle or coating. Advantageous properties associated with the use of protective vesicles and coatings include, for example, enhancing drug absorption and/or altering drug solubility. In this context, the drug in combination with either agent is continuously and gradually released from the gastric-retentive system to bathe the duodenum and the remainder of the small intestine in a prolonged manner which is determined by the rate at which the polymer erodes.

Examples of such vesicles include liposomes, which can protect an incorporated drug from the time it leaves the dosage form until it reaches the absorption site. Methods for preparing liposome encapsulated drug systems are known to and used by those of skill in the art. A general discussion, which includes an extensive bibliography regarding liposomes and methods for their preparation, can be found in "*Liposomes, A Practical Approach*," R. R. C New, Ed., 1990. Further examples of suitable vesicles include microparticulate systems, which are exemplified by nanoparticles and proteinoid and amino acid microspheres and pharmacosomes. Nanoparticles include, for example, nanospheres, nanocapsules, and nanocrystals. The matrix-like structure of the nanosphere allows the drug to be contained either within the matrix or coated on the outside. Nanoparticles may also consist of stabilized submicron structures of drug with or without surfactant or polymeric additives. Nanocapsules have a shell of polymeric material and, as with the nanospheres, the drug can be contained either within the shell or coated on the outside. Polymers that can be used to prepare the nanoparticles include, but are not limited to, polyacrylamide, poly(alkyl methacrylates), poly(alkyl cyanoacrylates), polyglutaraldehyde, poly(lactide-co-glycolide) and albumin. For details pertaining to nanoparticle preparation, see, e.g., Allemann, E., et al., "Drug-Loaded Nanoparticles—Preparation Methods and Drug Targeting Issues," *Eur. J. Pharm. Biopharm.* 39(5):173-191, 1993.

The dosage forms of the invention may also be formulated as bilayer tablets, trilayer tablets, or shell-and-core tablets, with bilayer and trilayer tablets preferred. In any of these embodiments wherein a dosage form is composed of two or more discrete regions each with different functions or attributes (e.g., a bilayer tablet with one layer being primarily swellable, and the other layer being primarily erodible), two or more drugs can be delivered in two or more different regions (e.g., layers), where the polymer or polymers in each region are tailored to provide a dissolution, erosion and/or release profile, taking the solubility and molecular weight of the drug into account. For example, a bilayer tablet may be prepared with one drug incorporated into an erosional layer and a second drug, which may or may not be identical to the first drug, incorporated into a swelling layer, or a single drug may be incorporated into an erosional layer, with no active agent in the swelling layer. As another example, a trilayer tablet may be prepared with a two outer layers containing drug, comprised of a polymer that is primarily erodible, with

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a swellable intermediate layer therebetween. The function of the swelling layer is to provide sufficient particle size throughout the entire period of drug delivery to promote gastric retention in the fed mode. In other embodiments, a drug may be included in a coating for immediate release.

VI. Dosage and Administration:

Different drugs have different biological half-lives, which determine their required frequency of administration (once daily, four times daily, etc.). Thus, when two or more drugs are co-administered in one conventional medication unit, an unfavorable compromise is often required, resulting in an underdose of one drug and an overdose of the other. One of the advantages of the dosage forms of the present invention is that they can be used to deliver multiple drugs without requiring such compromises. For example, in an alternative embodiment, a plurality of drug-containing, spherical, spheroidal- or cylindrical-shaped particles are provided, some of the particles containing a first drug/polymer composition designed to release the first drug at its ideal rate and duration (dose), while other particles contain a second drug/polymer composition designed to release the second drug at its ideal rate and duration. In this embodiment, the polymers or polymer molecular weight values used for each of the drugs can be the same or different. Control of the release rate of the differing drugs can also be obtained by combining different numbers of each of the drug/polymer particles in a common dosage form such as a capsule. For example, where two drugs are combined in a capsule made from five particles, three particles would contain one drug and the other two particles would contain the other drug.

Furthermore, the invention provides dosage forms of separate particles, each comprising polymers that may erode at different rates. As a result, the dosage forms of the present invention achieve a plurality of drug delivery rates. For example, the dosage form may comprise three particles, the first and second containing a swellable polymer that erodes and delivers drug over a period of 4 hours, and the third containing a swellable polymer that erodes and delivers drug over a period of 8 hours. In this regard, requisite erosion rates can be achieved by combining polymers of differing erosion rates into a single particle.

In addition, the invention provides dosage forms of separate particles, some comprising polymers that swell, but do not erode and some comprising polymers that swell and erode (with either the same or differing erosion rates). As a result, the dosage forms can achieve a plurality of delivery rates. For example, the dosage form may comprise three particles, the first containing a swellable polymer that delivers drug over a period of 8 hours, the second containing a swellable/erodible polymer that erodes and delivers drug over a period of 4 hours, and the third containing a swellable/erodible polymer that erodes and delivers drug over a period of 6 hours. In this example, the dosage form may contain one, two or three different drugs.

Drugs that are otherwise chemically incompatible when formulated together can be delivered simultaneously via separate swellable particles contained in a single dosage form. For example, the incompatibility of aspirin and prednisolone can be overcome with a dosage form comprising a first swellable particle with one drug and a second swellable particle with the other. In this manner, the gastric retention and simultaneous delivery of a great number of different drugs is now possible.

The dose of drugs from conventional medication forms is specified in terms of drug concentration and administration frequency. In contrast, because the dosage forms of the present invention deliver a drug by continuous, controlled release, a dose of medication used in the disclosed systems is specified by drug release rate and by duration of release. The continuous, controlled delivery feature of the system allows

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for (a) a reduction in drug side effects, since only the level needed is provided to the patient, and (b) a reduction in the number of doses per day.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the examples that follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

All patents, patent applications, and publications mentioned herein are hereby incorporated by reference in their entireties.

EXAMPLE 1

Drug dosage forms containing ciprofloxacin hydrochloride were prepared in the form of compressed tablets comprised of swellable, erodible matrix particles with the active agent therein. The matrix particles in the tablets were formulated so as to contain, in a 950 mg tablet, 582 mg ciprofloxacin hydrochloride (equivalent to 500 mg ciprofloxacin), at least one poly(ethylene oxide) (number average molecular weight indicated below), magnesium stearate or stearic acid as a lubricant, and optionally a poly(vinylpyrrolidone) (PVP) binder. The formulation of each dosage form was as follows:

Formulation GR-1 (caplet, 8.75×6.35×19.09 mm):

61.35 wt. % ciprofloxacin HCl

14.78 wt. % Polyox® 8 WSR N-60K

21.87 wt. % Polyox® WSR N-80

2 wt. % stearic acid

Formulation GR-2 (caplet, 8.75×6.43×19.09 mm):

61.35 wt. % ciprofloxacin HCl

36.65 wt. % Polyox® WSR N-60K

2 wt. % stearic acid

Formulation GR-3 (oval tablet, 10.05×7.15×18.05 mm):

61.66 wt. % ciprofloxacin HCl

34.43 wt. % Polyox® WSR N-60K

1.9 wt. % poly(vinyl pyrrolidone) (PVP)

2 wt. % magnesium stearate

Immediate Release (IR) Formulation (caplet, 8.75×6.35×19.09 mm):

500 mg ciprofloxacin tablet (Cipro®, obtained from Bayer Corporation)

The first two formulations were chosen based on the disintegration profile with the expectation that one of the formulations would be retained and deliver ciprofloxacin in the stomach for approximately four hours. These two formulations, as well as the immediate release tablet, were caplet shaped. The third formulation was in the shape of an oval instead of a caplet. The granulation for the oval formulation utilized a PVP binder solution, instead of a Polyox® WSR N-60K binder.

The in vitro release profiles of the dosage forms were evaluated using a USP Dissolution Test and a USP Disintegration Test. Specifically, each dosage form was individually tested in a USP Dissolution Apparatus II using the USP Dissolution Test described in USP 24-NF 19, Supplement 4, Section 711, using 900 mL of deionized water in a 1-liter vessel, anti-evaporation covers, a paddle speed of 100 rpm, and, for purposes of comparison, a paddle speed of 30 rpm. The disintegration test was carried out in a USP Disintegration Apparatus (55-mm stroke at 30 strokes/min) with fluted disks in place. In vivo pharmacokinetic properties were determined by administering one tablet to each of three human subjects within 5 minutes after consumption of a 350-calorie, high fat standardized meal. Ciprofloxacin absorption was measured by urinary excretion sampled at time intervals of 0, 1, 2, 4, 6, 8, 10, 12 hours and all urine voids up to 48 hours

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after dosing, collected in 12-hour intervals. Approximately 3 hours later, the subjects consumed a standardized lunch.

Table 1 and FIGS. 1 and 2 summarize the in vitro release characteristics of the four dosage forms.

TABLE 1

In Vitro Release Characteristics		
FORMULATION	RELEASE BY DISSOLUTION (% DRUG RELEASED @ X HOURS)	RELEASE BY DISINTEGRATION (TIME FOR 90% OF THE DOSAGE FORM TO DISINTEGRATE, "T ₉₀ ," IN HOURS)
GR-1	78% @ 8 hrs	3.3
GR-2	62% @ 8 hrs	5.9
GR-3	50% @ 8 hrs	82% released @ 8 hrs
IR (Cipro ®)	12 minutes	3 minutes

Table 2 summarizes the maximum urinary excretion rate of ciprofloxacin from the subjects in the in vivo tests. In general, the maximum urinary excretion rate was lower for all GR dosage forms in comparison with the immediate release tablet, and in fact decreased with increasing in vitro release profile. On the other hand, the t_{max} for the GR dosage forms was more than double that of the immediate release dosage form, indicative of an in vivo extended release profile.

TABLE 2

Summary of Individual Results								
SUBJECT	IR TABLET		GR-1		GR-2		GR-3	
	Max. Urinary Excretion (mg/hr)	t_{max} (hrs)	Max. Urinary Excretion (mg/hr)	t_{max} (hrs)	Max. Urinary Excretion (mg/hr)	t_{max} (hrs)	Max. Urinary Excretion (mg/hr)	t_{max} (hrs)
1	37.4	3.0	42.3	3.0	28.4	3.0	13.7	3.0
2	33.2	1.5	25.4	5.0	21.5	9.0	13.2	6.5
3	36.0	1.5	24.6	9.0	19.3	9.0	19.5	10
Average	35.5 ± 2.1	2.0	30.8 ± 10.0	5.7	23.1 ± 4.7	7.0	15.5 ± 6.5	6.5

The average relative bioavailability for the four dosage forms is shown in Table 3. The dose of the immediate release tablet was measured to be 519 mg ciprofloxacin per tablet, instead of the labeled 500 mg. With this taken into account, the relative bioavailability of the GR-1 and GR-2 caplets was equivalent to that of the immediate release tablet.

TABLE 3

Summary of Bioavailability and t_{max} Results				
Subject	IR Tablet	GR-1	GR-2	GR-3
Relative Bioavailability	39.70 ± 0.05%	39.29 ± 0.06%	37.40 ± 0.05%	21.30 ± 0.09%
t_{max}	2.0 ± 0.9 hrs	5.7 ± 3.1 hrs	7.0 ± 3.5 hrs	6.5 ± 3.5 hrs

FIGS. 3 and 4 show the difference in absorption from the four dosage forms in the three subjects. As may be seen, the GR dosage forms did exhibit extended release profiles, and the AUC's were generally comparable to the IR tablet.

EXAMPLE 2

The results of the above in vivo study indicated that the release profile of the GR dosage form should be optimized to take advantage of the average gastric residence time. The individual results from the three subjects showed a high

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degree of variability, due in part to the variability in the rate of drug release from the tablet (i.e., the difference between the disintegration and dissolution release profiles). In order to minimize patient-to-patient variability, formulations were modified so that the in vitro release profile obtained using a disintegration test would approximate the dissolution release profile.

The evaluation procedures were the same as those described above, and the formulations together with the symbols used in FIG. 5 where the results are plotted, were as follows:

Squares, solid line: Dissolution test results for 81.62 wt. % ciprofloxacin HCl, 13.86 wt. % Polyox® WSR N-60K, 2.52 wt. % PVP, 2.0 wt. % magnesium stearate.

Tablet dimensions of 10.03×5.94×16.09 mm, tablet weight of 666 mg (containing 544 mg ciprofloxacin HCl), N=6.

Squares, dashed line: Disintegration test results for 81.62 wt. % ciprofloxacin HCl, 13.86 wt. % Polyox® WSR N-60K, 2.52 wt. % PVP, 2.0 wt. % magnesium stearate.

Tablet dimensions of 10.03×5.94×16.09 mm, tablet weight of 666 mg (containing 544 mg ciprofloxacin HCl), N=6.

Triangle, solid line: Dissolution test results for 69.38 wt. % ciprofloxacin HCl,

11.78 wt. % Polyox® WSR N-60K, 15% microcrystalline cellulose (MCC), 2.14 wt. % PVP, 1.7 wt. % magnesium stearate.

Tablet dimensions of 0.03×5.76×16.06 mm, tablet weight of 800 mg (containing 555 mg ciprofloxacin HCl), N=6.

Triangle, dashed line: Disintegration test results for 69.38 wt. % ciprofloxacin HCl,

11.78 wt. % Polyox® WSR N-60K, 15% microcrystalline cellulose (MCC), 2.14 wt. % PVP, 1.7 wt. % magnesium stearate.

Tablet dimensions of 10.03×5.76×6.06 mm, tablet weight of 800 mg (containing 555 mg ciprofloxacin HCl), N=6.

Circles, solid line: Dissolution test results for 61.35 wt. % ciprofloxacin HCl,

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14.78 wt. % Polyox® WSR N-60K, 21.87 wt. % Polyox® WSR N-80, 2.0 wt. % stearic acid. Tablet dimensions of 8.75×6.45×19.01 mm, tablet weight of 901 mg (containing 553 mg ciprofloxacin HCl), N=3.

Circles, dashed line: Disintegration test results for 61.35 wt. % ciprofloxacin HCl, 14.78 wt. % Polyox® WSR N-60K, 21.87 wt. % Polyox® WSR N-80, 2.0 wt. % stearic acid. Tablet dimensions of 8.75×6.45×19.01 mm, tablet weight of 901 mg (containing 553 mg ciprofloxacin HCl), N=3.

X's, solid line: Dissolution test results for 60.82 wt. % ciprofloxacin HCl, 9 wt. % Polyox® 301, 25.65 wt. % Polyox® WSR N-80, 2.53 wt. % PVP, 2.0 wt. % magnesium stearate. Tablet dimensions of 12.04×6.24×19.06 mm, tablet weight of 909 mg (containing 553 mg ciprofloxacin HCl), N=3.

X's, dashed line: Disintegration test results for 60.82 wt. % ciprofloxacin HCl, 9 wt. % Polyox® 301, 25.65 wt. % Polyox® WSR N-80, 2.53 wt. % PVP, 2.0 wt. % magnesium stearate. Tablet dimensions of 12.04×6.24×19.06 mm, tablet weight of 909 mg (containing 553 mg ciprofloxacin HCl), N=3.

The formulation containing 13.86% Polyox® N-60K showed a 3-4 hour disintegration profile and approximately 9-hour dissolution profile. When the tablet size was increased to 900-mg and the ratio of drug to Polyox® N-60K was kept constant (using MCC as filler), the increase in tablet size resulted in a slower release rate, both for disintegration (approximately 5 hours) and dissolution (76% at 8 hours). The formulation containing 9% Polyox® 301/25.65% Polyox® N-80 showed a faster disintegration release of 2-3 hours and a dissolution release profile of approximately 8 hours. The presence of Polyox® N-80 appeared to act as an effective tablet disintegrant, while the Polyox® 301 provided tablet integrity. Also, while the Polyox® 301 prevented the tablet from disintegrating too quickly, the Polyox® N-80 allowed for a diffusional release from the tablet matrix.

FIG. 6 summarizes the data obtained with bi-layer and tri-layer ciprofloxacin HCl tablets. The bi-layer tablets contained an active layer and a 300-mg swelling layer (Polyox® 303). The tri-layer tablets contained active layers on the top and bottom with a 300-mg Polyox® 303 layer in the middle. The evaluation procedures were the same as those described above, and the formulations together with the symbols used in FIG. 6 where the results are plotted, were as follows:

Circles, solid line: Dissolution test results for bilayer tablet, with layer 1 containing 60.67 wt. % ciprofloxacin HCl, 34.8 wt. % Polyox® WSR N-80, 2.53 wt. % PVP, 2.0 wt. % magnesium stearate, and layer 2 containing 300 mg Polyox® 303. Tablet weight of 1213 mg (containing 554 mg ciprofloxacin HCl), tablet dimensions of 12.02×7.85×19.03 mm, N=3.

Circles, dashed line: Disintegration test results for bilayer tablet, with layer 1 containing 60.67 wt. % ciprofloxacin HCl, 34.8 wt. % Polyox® WSR N-80, 2.53 wt. % PVP, 2.0 wt. % magnesium stearate, and layer 2 containing 300 mg Polyox® 303. Tablet weight of 1213 mg (containing 554 mg ciprofloxacin HCl), tablet dimensions of 12.02×7.85×19.03 mm, N=3.

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Triangle, solid line: Dissolution test results for bilayer tablet, with layer 1 containing 60.67 wt. % ciprofloxacin HCl, 25 wt. % Polyox® WSR N-80, 9.8 wt. % Avicel® PH-101 (MCC), 2.53 wt. % PVP, 2.0 wt. % magnesium stearate, and layer 2 containing 300 mg Polyox® 303. Tablet weight of 1217 mg (containing 556 mg ciprofloxacin HCl), tablet dimensions of 12.03×7.79×19.05 mm, N=3.

Triangle, dashed line: Disintegration test results for bilayer tablet, with layer 1 containing 60.67 wt. % ciprofloxacin HCl, 25 wt. % Polyox® WSR N-80, 9.8 wt. % Avicel® PH-101 (MCC), 2.53 wt. % PVP, 2.0 wt. % magnesium stearate, and layer 2 containing 300 mg Polyox® 303. Tablet weight of 1217 mg (containing 556 mg ciprofloxacin HCl), tablet dimensions of 12.03×7.79×19.05 mm, N=3.

X's, solid line: Dissolution test results for trilayer tablet, with outer layers each containing 46.08 wt. % ciprofloxacin HCl, 10 wt. % Polyox® 301, 40 wt. % Polyox® WSR N-80, 1.92 wt. % PVP, and 2.0 wt. % magnesium stearate, and middle layer containing 300 mg Polyox® 303. Tablet dimensions of 12.00×6.36×19.03 mm, tablet weight of 901 mg (554 mg ciprofloxacin HCl), N=3.

X's, dashed line: Disintegration test results for trilayer tablet, with outer layers each containing 46.08 wt. % ciprofloxacin HCl, 10 wt. % Polyox® 301, 40 wt. % Polyox® WSR N-80, 1.92 wt. % PVP, and 2.0 wt. % magnesium stearate, and middle layer containing 300 mg Polyox® 303. Tablet dimensions of 12.00×6.36×19.03 mm, tablet weight of 901 mg (containing 554 mg ciprofloxacin HCl), N=3.

EXAMPLE 3

Two formulations (500 mg) of gastric retentive tablets of ciprofloxacin hydrochloride were fabricated under GMP conditions at MDS Pharma Services (Tampa, Fla.). To ensure that ciprofloxacin would not be delivered to the colon, the period of 90% drug release in USP Type I dissolution testing (0.1 N HCl, 100 rpm, pH=1) was designed to be approximately 6 hours. Since retention and drug release represent a balance between swelling and erosion, respectively, 2 formulations were selected. One formulation involved conventional tabletting (GR-A) and the other swelled to a greater extent to ensure retention, but was more difficult to manufacture (GR-B). Immediate release tablets (500 mg, Cipro®, Bayer) were used as obtained. The compositions of GR-A and GR-B are given below.

GR-A: 74.26 wt. % ciprofloxacin HCl, 20 wt. % Polyox® 1105, 4.74 wt. % PVP, 1.0 wt. % magnesium stearate. Tablet dimensions of 10.1×6.5×18.1 mm, tablet weight of 796 mg (containing 508 mg ciprofloxacin).

GR-B: Layer 1: 59.41 wt. % ciprofloxacin HCl, 35.8 wt. % Polyox® WSR-N80, 3.79 wt. % PVP, 0.99 wt. % magnesium stearate. Layer 2: 300 mg Polyox® 303.

Tablet dimensions of 12.05×7.9×19.05 mm, tablet weight of 1280 mg (containing 500 mg ciprofloxacin).

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Immediate Release (IR) Formulation (caplet, 8.75×6.35×19.09 mm):

500 mg ciprofloxacin tablet (Cipro®, obtained from Bayer Corporation)

The dissolution and disintegration profiles obtained in vitro as described in Example 1 are plotted in FIG. 7. The procedure was repeated using a bicarbonate buffered media (pH=6.8) instead of the 0.1 N HCl solution, and the results are plotted in FIG. 8. The procedure was substantially repeated using mammalian simulated intestinal fluid (mSIF) instead of the 0.1 N HCl solution, and Table 4 shows the percent of ciprofloxacin release from the GR-A formulation at 1 and 6 hours. The GR-A formulation represented a 6-hour system with over 90% drug release in 0.1 N HCl.

TABLE 4

Dissolution of Ciprofloxacin GR-A Tablets		
Receptor Media	Percent Released (%)	
	1 hour	6 hour
0.1N HCl	15.2	91.6
mSIF	0.9	3.1
Bicarbonate Buffer	0.5	3.4

An analytical test was performed on the solubility of ciprofloxacin in three different solutions, deionized water (DI), mSIF, and a bicarbonate-buffered solution. Ciprofloxacin was added to each solvent gradually until the solution became saturated. Each mixture was then centrifuged and the concentration of ciprofloxacin in the supernatant was analyzed by high performance liquid chromatography. The results are provided in Table 5.

TABLE 5

Solubility of Ciprofloxacin Hydrochloride			
Receptor Media	pH Before adding Ciprofloxacin HCl	pH After Adding Ciprofloxacin HCl	Solubility of Ciprofloxacin HCl (mg/mL)
Deionized Water	5.8	3.8	30
mSIF	6.8	6.7	0.1
Bicarbonate Buffer	6.8	8.2	0.1

Ciprofloxacin was found to be very insoluble in both mSIF and bicarbonate-buffered solution (pH=6.8).

EXAMPLE 4

The pharmacokinetics of two formulations of gastric retentive tablets of ciprofloxacin hydrochloride and the immediate release tablet (Cipro® 500 mg base) were compared in 15 healthy volunteers. Retention in the stomach in the fed mode was based on polymeric swelling, and drug release was based on polymeric erosion. Extended release profiles were observed for the gastric retentive tablets with comparable bioavailability to the immediate release tablet.

A single dose, 3-way, open-label, randomized crossover study was conducted under GCP in 15 healthy volunteers at the AAI facility in Neu-Ulm, Germany. All treatments were administered within 5 minutes after a 500-calorie, moderate fat breakfast. There was a 5-day wash out period between treatments. All volunteers were screened and signed informed consent forms prior to enrolling in the study. Plasma samples

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were taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dosing. Urine was collected for 36 hours. Ciprofloxacin was analyzed in plasma and urine by HPLC. Noncompartmental parameters were calculated for the plasma data. Statistical differences were detected by ANOVA ($p < 0.05$).

The mean \pm S.D. for the pharmacokinetic parameters for each treatment is reported in Table 6. There were no statistical differences in AUC among treatments. The mean bioavailabilities of the two gastric retentive tablets were approximately 90% relative to the immediate release tablet. Statistical differences were detected in terms of a reduction of C_{max} and a greater t_{max} for the gastric retentive tablets compared to the immediate release tablet. No statistical differences were observed between the 2 gastric retentive tablets. Both gastric retentive tablets yielded extended release plasma profiles without significant loss of bioavailability. Plasma profiles in terms of plasma levels versus time are plotted in FIG. 9. In this study, there was a trend toward less variability with the GR-B tablet, but this difference is well within experimental variation. The intersubject variation in delivery for both gastric retentive tablets was comparable to the variation for the immediate release tablet.

TABLE 6

Noncompartmental PK Parameters for Treatments				
Treatment	AUC (ng·h/ml)	Relative Bioavailability	Cmax (ng/ml)	Tmax (h)
IR	7320 \pm 2030	—	1780 \pm 580	1.2 \pm 0.7
GR-A	6420 \pm 2340	0.88 \pm 0.21	1090 \pm 410***	3.6 \pm 2.0***
GR-B	6790 \pm 2350	0.92 \pm 0.17	1030 \pm 390***	3.7 \pm 1.5***

*** $p < 0.001$

All three treatments were well tolerated and the adverse reactions were mild and appear drug related. Both gastric retentive tablets provided extended duration of plasma for ciprofloxacin and had comparable bioavailability to the immediate release tablet.

We claim:

1. A method for delivering a pharmacologically active agent, the method comprising:

orally administering to a patient in a fed mode a matrix/active agent tablet dosage form comprised of a polymer matrix and the pharmacologically active agent dispersed in said polymer matrix, said polymer matrix comprised of a biocompatible, hydrophilic polymer which

(a) upon imbibition of water swells unrestrained dimensionally to a size effective to promote gastric retention for a time period of about 4 to 9 hours, and

(b) maintains its size for the time period before it is diminished by erosion,

wherein at least 75 wt. % of the active agent in the dosage form is released by erosion of the polymer matrix within the time period.

2. The method of claim 1, wherein at least 85 wt. % of the active agent in the dosage form is released within the time period.

3. The method of claim 1, wherein the dosage form is characterized by an erosion rate (ER) to dissolution rate (DR) ratio of approximately 1.1:1 to 5:1, wherein ER is the rate of active agent release in an aqueous medium measured using an in vitro disintegration test, and DR is the rate of active agent release in an aqueous medium measured using an in vitro dissolution test.

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4. The method of claim 1, wherein the dosage form is characterized by an ER to DR ratio of approximately 1.2:1 to approximately 3:1.

5. The method of claim 4, wherein the dosage form is characterized by an ER to DR ratio of approximately 1.3:1 to approximately 2:1.

6. The method of claim 5, wherein the dosage form is characterized by an ER to DR ratio of approximately 1.5:1 to approximately 2:1.

7. The method of claim 1, wherein the matrix-active agent tablet comprises a therapeutically effective amount of the pharmacologically active agent.

8. The method of claim 7, wherein the therapeutically effective amount of the active agent in the dosage form is in a range of about 0.01% to 80% by volume.

9. The method of claim 8, wherein the therapeutically effective amount of the active agent in the dosage form is in a range of about 60% to about 80% of the dosage form by volume.

10. The method of claim 9, wherein the therapeutically effective amount of the active agent in the dosage form is approximately 60% by volume.

11. The method of claim 1, wherein said active agent possesses an aqueous solubility that decreases with increasing pH.

12. The method of claim 11, wherein following administering of said dosage form and gastric retention thereof, the dosage form passes into the lower gastrointestinal tract, whereby active agent remaining in the dosage form is insoluble and unavailable for absorption.

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13. The method of claim 1, wherein the active agent is an antibiotic.

14. The method of claim 13, wherein the active agent is selected from the group consisting of ciprofloxacin, minocycline, and acid addition salts thereof.

15. The method of claim 14, wherein the active agent is ciprofloxacin.

16. The method of claim 14, wherein the active agent is ciprofloxacin hydrochloride.

17. The method of claim 14, wherein the active agent is minocycline.

18. The method of claim 14, wherein the active agent is minocycline hydrochloride.

19. The method of claim 1, wherein the active agent is selected from the group consisting of furosemide, gabapentin, losartan, and budesonide.

20. The method of claim 1, wherein the active agent is gabapentin.

21. A method for treating a human patient suffering from a bacterial infection that is responsive to the oral administration of ciprofloxacin, comprising orally administering to the subject in a fed mode a therapeutically effective amount of the dosage form of claim 1.

22. The method of claim 21, wherein the dosage form is administered once daily.

23. The method of claim 21, wherein the bacterial infection is infection with mycobacterium avium complex, *Pseudomonas*, *Shigella*, *Salmonella*, toxigenic *E. coli*, *Campylobacter*, *Enterobacter*, or *Bacillus anthracis*.

* * * * *

EXHIBIT G

US008668929B2

(12) **United States Patent**
Han et al.(10) **Patent No.:** **US 8,668,929 B2**
(45) **Date of Patent:** **Mar. 11, 2014**(54) **GASTRIC RETENTIVE
EXTENDED-RELEASE DOSAGE FORMS
COMPRISING COMBINATIONS OF A
NON-OPIOID ANALGESIC AND AN OPIOID
ANALGESIC**(75) Inventors: **Chien-Hsuan Han**, Sunnyvale, CA
(US); **Sui Yuen Eddie Hou**, Foster City,
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CA (US)(73) Assignee: **Depomed, Inc.**, Newark, CA (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **13/529,960**(22) Filed: **Jun. 21, 2012**(65) **Prior Publication Data**

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11, 2008.(51) **Int. Cl.**
A61K 9/26 (2006.01)(52) **U.S. Cl.**
USPC **424/469**(58) **Field of Classification Search**
USPC **424/469**
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

4,713,243	A	12/1987	Schiraldi et al.
4,851,226	A	7/1989	Julian et al.
4,894,236	A	1/1990	Jang et al.
4,996,058	A	2/1991	Sinnreich
5,075,114	A	12/1991	Roche
5,266,331	A	11/1993	Oshlack et al.
5,336,691	A	8/1994	Raffa et al.
5,478,577	A	12/1995	Sackler et al.
5,508,042	A	4/1996	Oshlack et al.
5,549,912	A	8/1996	Oshlack et al.
5,582,837	A	12/1996	Shell
5,626,874	A	5/1997	Conte et al.
5,656,295	A	8/1997	Oshlack et al.
5,672,360	A	9/1997	Sackler et al.
5,783,212	A	7/1998	Fassihi et al.
5,866,161	A	2/1999	Childers et al.
5,876,759	A	3/1999	Gowan, Jr.
5,891,471	A	4/1999	Miller et al.
5,945,123	A	8/1999	Hermelin
5,945,125	A	8/1999	Kim
5,958,459	A	9/1999	Chasin et al.
5,965,161	A	10/1999	Oshlack et al.
5,965,163	A	10/1999	Miller et al.

5,965,167	A	10/1999	Sanghvi et al.
5,968,551	A	10/1999	Oshlack et al.
5,972,389	A	10/1999	Shell et al.
5,980,882	A	11/1999	Eichman
6,024,982	A	2/2000	Oshlack et al.
6,068,855	A	5/2000	Leslie et al.
6,071,208	A	6/2000	Koivunen
6,103,219	A	8/2000	Sherwood et al.
6,103,261	A	8/2000	Chasin et al.
6,126,969	A	10/2000	Shah et al.
6,143,322	A	11/2000	Sackler et al.
6,210,714	B1	4/2001	Oshlack et al.
6,245,357	B1	6/2001	Edgren et al.
6,254,887	B1	7/2001	Miller et al.
6,340,475	B2	1/2002	Shell et al.
6,348,216	B1	2/2002	Kushla et al.
6,372,254	B1	4/2002	Ting et al.
6,375,957	B1	4/2002	Kaiko et al.
6,387,404	B2	5/2002	Oshlack et al.
6,488,962	B1	12/2002	Berner et al.
6,488,963	B1	12/2002	McGinity et al.
6,491,945	B1	12/2002	Childers et al.
6,500,459	B1	12/2002	Chhabra et al.
6,599,529	B1	7/2003	Skinhoj et al.
6,635,280	B2	10/2003	Shell et al.
6,667,060	B1	12/2003	Vandecruys et al.
6,682,759	B2	1/2004	Lim et al.
6,696,066	B2	2/2004	Kaiko et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0159852	A2	10/1985
EP	0305051	A1	3/1989

(Continued)

OTHER PUBLICATIONS

Gafourian (Journal of Pharmaceutical Sciences, vol. 96, No. 12, Dec. 2007).*

Sirkia (STP Pharma Sciences, 3 (6) 453-458).*

Kim (Drug Development and Industrial Pharmacy, 24(7), 645-651 (1998).*

Jagdale (AAPS PharmSciTech, vol. 10, No. 3, Sep. 2009).*

Childs, FDA panel urges cuts in acetaminophen doSage, ABC News, Jun. 30, 2009, Retrieved from the internet <URL: <http://abcnews.go.com/Health/PainManagement/story?id=7965902&page=1>>, 3 pages.

Divoll e al., "Effect of food on acetaminophen absorption in young and elderly subject", J. Clin. Pharmacol., vol. 22, No. 11-12, pp. 571-576 (1982).

International Search Report from PCT Patent Application No. PCT/US2010/047369 mailed May 30, 2011, application now published as PCT Publication No. WO 2011/026125 on Mar. 3, 2011.

(Continued)

Primary Examiner — David J Blanchard*Assistant Examiner* — Devang Thakor(74) *Attorney, Agent, or Firm* — McDermott Will & Emery LLP(57) **ABSTRACT**

Compositions and methods for the treatment of pain in a mammal are described. More specifically, a dosage form designed for release of acetaminophen and an opioid is described, wherein the dosage form provides delivery of the drugs to the upper gastrointestinal tract ("GI") of a mammal for an extended period of time.

42 Claims, 15 Drawing Sheets

US 8,668,929 B2

Page 2

(56)

References Cited

U.S. PATENT DOCUMENTS

6,706,281 B2 3/2004 Oshlack et al.
 6,723,340 B2 4/2004 Gusler et al.
 6,730,321 B2 5/2004 Ting et al.
 6,733,783 B2 5/2004 Oshlack et al.
 6,797,283 B1 9/2004 Edgren et al.
 6,852,336 B2 2/2005 Hunter et al.
 6,902,742 B2 6/2005 Devane et al.
 7,074,430 B2 7/2006 Miller et al.
 7,201,920 B2 4/2007 Kumar et al.
 7,374,781 B2 5/2008 Zhang et al.
 7,405,238 B2 7/2008 Markey et al.
 7,413,751 B2 8/2008 Devane et al.
 7,438,927 B2 10/2008 Berner et al.
 7,514,100 B2 4/2009 Oshlack et al.
 7,674,799 B2 3/2010 Chapman et al.
 7,683,072 B2 3/2010 Chapman et al.
 7,691,873 B2 4/2010 Duncalf et al.
 7,776,314 B2 8/2010 Bartholomäus et al.
 7,846,476 B2 12/2010 Oshlack et al.
 7,897,172 B2 3/2011 Qasem et al.
 7,939,543 B2 5/2011 Kupper
 7,943,170 B2 5/2011 Chan et al.
 7,976,870 B2 7/2011 Berner et al.
 8,075,872 B2 12/2011 Arkenao-Maric et al.
 2001/0008639 A1 7/2001 Oshlack et al.
 2002/0018810 A1 2/2002 Oshlack et al.
 2002/0058050 A1 5/2002 Sackler et al.
 2002/0192277 A1 12/2002 Oshlack et al.
 2003/0035837 A1 2/2003 Sackler et al.
 2003/0044466 A1* 3/2003 Markey et al. 424/469
 2003/0091635 A1 5/2003 Baichwal et al.
 2003/0092724 A1* 5/2003 Kao et al. 514/282
 2003/0099704 A1 5/2003 Oshlack et al.
 2003/0104062 A1 6/2003 Berner et al.
 2003/0180361 A1 9/2003 Oshlack et al.
 2003/0235616 A1 12/2003 Sowden et al.
 2004/0096500 A1 5/2004 Oshlack et al.
 2004/0105887 A1 6/2004 Oshlack et al.
 2004/0131671 A1 7/2004 Zhang et al.
 2004/0156899 A1 8/2004 Louie-Helm et al.
 2004/0202716 A1 10/2004 Chan et al.
 2004/0224020 A1 11/2004 Schoenhard
 2005/0013863 A1 1/2005 Lim et al.
 2005/0020613 A1 1/2005 Boehm et al.
 2005/0031546 A1 2/2005 Bartholomäus et al.
 2005/0089570 A1 4/2005 Cruz et al.
 2005/0106249 A1 5/2005 Hwang et al.
 2005/0112195 A1 5/2005 Cruz et al.
 2005/0158382 A1 7/2005 Cruz et al.
 2005/0165038 A1 7/2005 Gordon
 2005/0214251 A1 9/2005 Pohl et al.
 2005/0232987 A1 10/2005 Srinivasan et al.
 2005/0266032 A1 12/2005 Srinivasan et al.
 2005/0267189 A1 12/2005 Gao et al.
 2006/0002860 A1 1/2006 Bartholomäus et al.
 2006/0057210 A1 3/2006 Oshlack et al.
 2006/0099255 A1 5/2006 Oshlack et al.
 2006/0165791 A1 7/2006 Oshlack et al.
 2006/0193782 A1 8/2006 Bartholomäus et al.
 2006/0205752 A1 9/2006 Whitehead
 2006/0240105 A1 10/2006 Devane et al.
 2006/0251721 A1 11/2006 Cruz et al.
 2006/0263436 A1 11/2006 Baert et al.
 2006/0269604 A1 11/2006 Sackler et al.
 2006/0292214 A1 12/2006 Jenkins et al.
 2007/0020335 A1 1/2007 Chen et al.
 2007/0048228 A1 3/2007 Arkenau-Maric et al.
 2007/0059359 A1 3/2007 Backensfeld et al.
 2007/0128279 A1 6/2007 Edgren et al.
 2007/0183980 A1 8/2007 Arkenau-Maric et al.
 2007/0184112 A1 8/2007 Wong et al.
 2007/0190142 A1 8/2007 Breitenbach et al.
 2007/0207200 A1 9/2007 Plachetka et al.
 2007/0237816 A1 10/2007 Finkelstein
 2007/0237833 A1 10/2007 Sackler et al.

2007/0259033 A1 11/2007 Cruz
 2007/0259045 A1 11/2007 Mannion et al.
 2007/0275065 A1 11/2007 Oshlack et al.
 2007/0281018 A1 12/2007 Qiu et al.
 2008/0020039 A1 1/2008 Parikh et al.
 2008/0031901 A1 2/2008 Qiu et al.
 2008/0031963 A1 2/2008 Sackler et al.
 2008/0044482 A1 2/2008 Oshlack et al.
 2008/0057122 A1 3/2008 Toney-Parker et al.
 2008/0113025 A1 5/2008 Devane et al.
 2008/0132532 A1 6/2008 Wright et al.
 2008/0138422 A1 6/2008 Staniforth
 2008/0220062 A1 9/2008 Ashton
 2009/0022798 A1 1/2009 Rosenberg et al.
 2009/0028941 A1 1/2009 Cowles et al.
 2009/0068269 A1 3/2009 Oshlack et al.
 2009/0081290 A1 3/2009 McKenna et al.
 2009/0149479 A1 6/2009 Jenkins et al.
 2009/0155357 A1 6/2009 Muhuri
 2009/0175937 A1 7/2009 Rahmouni et al.
 2009/0202629 A1 8/2009 Oshlack et al.
 2009/0304793 A1 12/2009 Boehm
 2009/0306119 A1 12/2009 Keane
 2009/0311320 A1 12/2009 Ourey et al.
 2009/0317355 A1 12/2009 Roth et al.
 2009/0324714 A1 12/2009 Liu et al.
 2010/0010030 A1 1/2010 Jain et al.
 2010/0015222 A1 1/2010 Han et al.
 2010/0034876 A1 2/2010 Oshlack et al.
 2010/0040681 A1 2/2010 Park et al.
 2010/0092570 A1 4/2010 Oshlack et al.
 2010/0168148 A1 7/2010 Wright et al.
 2010/0172974 A1 7/2010 Oshlack et al.
 2010/0172989 A1 7/2010 Roth et al.
 2010/0196425 A1 8/2010 Cruz et al.
 2010/0196471 A1 8/2010 Jain et al.
 2010/0196474 A1 8/2010 Han et al.
 2010/0216829 A2 8/2010 Kumar et al.
 2010/0221293 A1 9/2010 Cruz et al.
 2010/0239662 A1 9/2010 Rahmouni et al.
 2010/0260833 A1 10/2010 Bartholomäus et al.
 2011/0020451 A1 1/2011 Bartholomäus et al.
 2011/0038927 A1 2/2011 Oshlack et al.
 2011/0038930 A1 2/2011 Barnscheid et al.
 2011/0052685 A1 3/2011 Hou et al.
 2011/0077238 A1 3/2011 Leech et al.
 2011/0117196 A1 5/2011 Gordon
 2011/0118189 A1 5/2011 Farr et al.
 2011/0129507 A1 6/2011 Cruz
 2011/0150969 A1 6/2011 Shah et al.
 2011/0150970 A1 6/2011 Shah et al.
 2011/0150971 A1 6/2011 Shah et al.
 2011/0150989 A1 6/2011 Park et al.
 2011/0150990 A1 6/2011 Shah et al.
 2011/0150991 A1 6/2011 Shah et al.
 2011/0159046 A1 6/2011 Cruz
 2011/0166171 A1 7/2011 Qiu et al.
 2011/0177168 A1 7/2011 Chan et al.
 2011/0195116 A1 8/2011 Hobbs et al.
 2011/0195989 A1 8/2011 Rudnic et al.
 2011/0207762 A1 8/2011 Chapman et al.
 2011/0212173 A1 9/2011 Young et al.
 2011/0229526 A1 9/2011 Rosenberg et al.
 2011/0229533 A1 9/2011 Edgren et al.
 2011/0262532 A1 10/2011 Oshlack et al.
 2011/0287095 A1 11/2011 Park et al.
 2011/0301129 A1 12/2011 Berner et al.
 2011/0318392 A1 12/2011 Cruz et al.
 2012/0321713 A1 12/2012 Han et al.

FOREIGN PATENT DOCUMENTS

EP 1140026 A1 6/2000
 WO 97/18814 A1 5/1997
 WO 98/55107 A1 12/1998
 WO 03/024426 A1 3/2003
 WO 2005/013863 A2 2/2005
 WO 2006/022759 3/2006
 WO 2006/071208 A1 7/2006

US 8,668,929 B2

Page 3

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	WO 2005/030182	A1	4/2007
WO	WO 2008/015221	A2	2/2008
WO	WO 2009/049405	A1	4/2009
WO	WO 2009/076764	A1	6/2009
WO	WO 2009/114648	A1	9/2009
WO	WO 2009/135846	A1	11/2009
WO	WO 2010/032128	A1	3/2010
WO	WO 2010/069050	A1	6/2010
WO	WO 2010/078486	A2	7/2010
WO	WO 2010/141505	A1	12/2010
WO	WO 2011/009603	A1	1/2011
WO	WO 2011/009604	A1	1/2011
WO	WO 2011/068723	A1	6/2011
WO	WO 2011/077451	A2	6/2011
WO	WO 2011/106416	A2	9/2011
WO	WO 2012/007159	A2	1/2012

OTHER PUBLICATIONS

Knovel, Merck Index; Metformin, Acetaminophen, and Vancomycin, Merck Sharp & Dohme Corp., copyright 2006, 2012, Download Aug. 9, 2012, Retrieved from the internet <URL: http://www.knovel.com/web/portal/basic_search/display?_EXT_KNOVEL_DISPLAY_bookid=1863>, 9 pages.

Rawlins et al., "Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration", *Eur. J. Clin. Pharmacol.*, vol. 11, No. 4, pp. 283-286 (1977).

Foremost NF Fast Flo Lactose, "A spray-dried mixture of crystalline and amorphous lactose", Foremost Farms USA, 1 pg., Online Article downloaded from the site: http://www.foremostfarms.com/Commercials/pdfs/Specifications/TDS_NF_Lactose_316.pdf, Document created on Jan. 28, 2010.

Freedet et al., "pH control of nucleophilic/electrophilic oxidation", *Int. J. Pharm.*, vol. 357, pp. 180-188 (2008).

Gammaitoni et al., "Randomized, Double-Blind, Placebo-Controlled Comparison of the Analgesic Efficacy of Oxycodone 10 mg/Acetaminophen 325 mg versus Controlled-Release Oxycodone 20 mg in Postsurgical Pain," *J. Clin. Pharmacol.*, vol. 43, pp. 296-304 (2003).

Hou et al., "Gastric retentive dosage forms: a review", *Crit. Rev. Ther. Drug carr. Sys.*, vol. 20, No. 8, pp. 461-497 (2003).

International Search Report from related PCT Patent application No. PCT/US2009/036864 mailed Aug. 31, 2009, application now published as PCT Publication No. WO2009/114648 on Sep. 17, 2009.

International Search Report from PCT Patent Application No. PCT/US2010/061400 mailed Nov. 25, 2011, application now published as PCT Publication No. WO 2011/087765 on Jul. 21, 2011.

James et al., "Acetaminophen-Induced Hepatotoxicity", *The American Society for Pharmacology and Experimental Therapeutics*, (2003), vol. 31, No. 12, pp. 1499-1506.

Khosla, et al., "The effect of tablet size on the gastric emptying of non-disintegrating tablets", *International Journal of Pharmaceutics*, vol. 62, pp. R9-R11 (1990).

Khosla et al., "Gastrointestinal transit of non-disintegrating tablets in fed subjects", *International Journal of Pharmaceutics*, vol. 53, pp. 107-117 (1989).

Kim "Effects of drug solubility, drug loading and polymer molecular weight on drug release from polyox tablets", *Drug. Dev. Ind. Pharm.*, vol. 24, No. 7, pp. 645-651 (1998).

Lab Basics Technical Library, Particle Size Conversion Table, Sigma-Aldrich, 3 pgs., Online Article downloaded from the site: <http://www.sigmaaldrich.com/chemistry/stockroom-reagents/learning-center/technical-library/particle-size-conversion.printerview.html> on Apr. 17, 2012.

Levy-Cooperman et al., "A novel extended-release formulation of oxycodone/acetaminophen with abuse deterrent properties", *Painweek*, 2 pgs., Online Article downloaded from the site: http://www.painweek.org/media/mediafile_attachments/06/26-pain20100131.pdf, Document created Aug. 28, 2010, Abstract Only.

Microchnitchenko et al., "Acetaminophen Toxicity", *The American Society for Biochemistry and Molecular Biology, Inc.*, vol. 274, No. 15, pp. 10349-10355 (1999).

Mitchell et al., "Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione", *J. Pharmacol. Exp. Ther.*, vol. 187, No. 187, No. 1, pp. 211-217 (1973).

Moes, "Gastroretentive dosage forms", *Rev. Ther. Drug Carr. Sys.*, vol. 10, No. 2, pp. 143-195 (1995).

Moller et al., "Time to Onset of Analgesia and Analgesic Efficacy of Effervescent Acetaminophen", *J. Clin. Pharmacol.*, vol. 40, pp. 370-378 (2000).

Nelson and Bruschi, "Mechanisms of Acetaminophen-Induced liver disease", *Drug Induced Liver Disease*, Kaplowitz et al., Ed., Marcel Dekker, Inc. New York, NY, Chapter 13, pp. 287-325 (2003).

Nielson et al., "Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol", *Eur. J. Clin. Pharmacol.*, vol. 42, pp. 261-264 (1992).

Nimmo et al., "Inhibition of gastric emptying and drug absorption by narcotic analgesics", *Br. J. Clin. Pharmac.*, vol. 2, pp. 509-513 (1975).

Oxycontin, "(Oxycodone HCl controlled-release) tablets", Description and Patient Information, Purdue Pharma, 32 pgs, Online Article downloaded from site: <http://www.purduepharma.com/pi/prescription/oxycontin.pdf>, Document created Aug. 17, 2010.

Percocet, "(Oxycodone and Acetaminophen Tablets, USP)", Package Insert, Endo Pharmaceuticals, 17 pgs., Online Article downloaded from the site: http://www.endo.com/File%20Library/Products/Prescribing%20Information/Percocet_pack_insert_2.pdf, Document created Jul. 11, 2011.

Polyox Water-Soluble Resins, Technical Data, "Degradation of water-soluble resins", Form 326-00027-1002AMS (2002).

Polyox Water-Soluble Resins, Technical Data, "Water-soluble resin storage stability", Form 326-00044-0704MAB (2004).

Rinaldi et al., "Minireview Reactive Intermediates and the Dynamics of Glutathione Transferases", *The American Society for Pharmacology and Experimental Therapeutics*, vol. 30, No. 10, pp. 1053-1058 (2002).

Rumack et al., "Acetaminophen Hepatotoxicity: The First 35 Years", *Clinical Toxicology*, vol. 40, No. 1, pp. 3-20 (2002).

Skoglund et al., "Efficacy of paracetamol-esterified menthionine versus cysteine or methionine on paracetamol-induced hepatic GSH depletion and plasma ALAT level in mice", *Biochem. Pharmacol.*, vol. 35, pp. 3071-3075, (1986).

Streuble et al., "Drug delivery to the upper small intestine window using gastroretentive technologies", *Curr. Opin. Pharm.*, vol. 6, pp. 501-508 (2006).

Streuble et al., "Gastroretentive drug delivery systems", *Expert Opin. Drug Del.*, vol. 3, No. 2, pp. 217-233 (2006).

Talukder and Fassihi, "Gastroretentive delivery systems: a mini review", *Drug Development and Industrial Pharmacy*, vol. 30, No. 10, pp. 1019-1028 (2004).

Tylenol *Acetaminophen* "Tylenol Professional Product Information", McNeil Consumer Healthcare, 62 pgs., Online article downloaded from the site: http://www.tylenolprofessional.com/assets/TYL_PPI.pdf, Document created Mar. 24, 2010.

U.S. Department of Health & Human Services, FDA Drugs Safety Communication. Prescription Acetaminophen Products to be Limited to 325mg per Dosage Unit, Boxed Warning Will Highlight Potential for Severe Liver Failure, 5 pgs., Online Article downloaded from the site: www.fda.gov/drugs/drugsafety/ucm239821.htm, Article Last Updated on Jan. 21, 2011.

Waterman et al., "Stabilization of pharmaceuticals to oxidative degradation", *Pharm. Dev. Tech.*, vol. 7, No. 1, pp. 1-32 (2002).

Zhang et al., "Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release", *Pharm. Dev. Tech.*, vol. 6, No. 2, pp. 131-144 (2001).

Zhu et al., "Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate", *Int. J. Pharm.*, vol. 241, No. 2, pp. 301-310 (2002).

Doteuchi et al., "Pharmacological studies of oxycodone hydrochloride. 1. Antinociceptive effect and general pharmacology", *Pharmacometrics*, vol. 49, No. 3, pp. 257-273 (1995).

US 8,668,929 B2

Page 4

(56)

References Cited

OTHER PUBLICATIONS

Meert et al., "A preclinical comparison between different opioids: antinociceptive versus adverse effects", *Pharmacol. Biochem. Behavior*, vol. 80, No. 2, pp. 309-326 (2005).

U.S. Appl. No. 13/360,595, filed Jan. 27, 2012, Han et al.

U.S. Appl. No. 13/473,563, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,571, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,578, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,584, filed May 16, 2012, Devarakonda et al.

U.S. Appl. No. 13/473,586, filed May 16, 2012, Devarakonda et al.

Altaf et al., "Bead compacts. II: Evaluation of rapidly disintegrating nonsegregating compressed bead formulations", *Drug Development and Industrial Pharmacy*, vol. 25, No. 5, pp. 635-642 (1999).

Banfai et al., "Content uniformity and assay requirements in current regulations", *J. Chromatogr. A.*, vol. 1156, No. 1-2, pp. 206-212 (2007).

Bardonnet et al., "Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*", *J. Controlled Rel.*, vol. 111, pp. 1-18 (2006).

Bartels et al., "Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial", *Clinical Toxicology*, vol. 46, pp. 243-249 (2008).

Boelsterli, "Mechanisms underlying the hepatotoxicity of nonsteroidal anti-inflammatory drugs", *Drug Induced Liver Disease*, Kaplowitz et al., Ed., Marcel Dekkar, Inc. New York, NY, Chapter 15, pp. 345-375 (2003).

Bolesta et al., "Hepatotoxicity Associated with Chronic Acetaminophen Administration in Patients without Risk Factors", *The Annals of Pharmacotherapy*, vol. 36, pp. 331-333 (2002).

Brzeznicka et al., "Dynamics of Glutathione Levels in Liver and Indicatory Enzymes in Serum in Acetaminophen Intoxication in Mice", *Polish Journal of Occupational Medicine*, vol. 2, No. 1, pp. 15-22 (1989).

Corcoran et al., "Role of Glutathione in Prevention of Acetaminophen-Induced Hepatotoxicity by N-Acetyl-L-Cysteine in

Vivo: Studies with N-Acetyl-D-Cysteine in Mice"; *The Journal of Pharmacology and Experimental Therapeutics*, vol. 238, No. 1, pp. 54-61 (1986).

Dart et al., "Acetaminophen Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management", (2006), *Clinical Toxicology*; 44, pp. 1-18 (2006).

Davis et al., "Species Differences in Hepatic Glutathione Depletion, Covalent Binding and Hepatic Necrosis after Acetaminophen", *Life Sciences*, vol. 14, pp. 2099-2109 (1974).

Davis et al., "The gastrointestinal transit of a controlled release formulation of indomethacin", *International Journal of Pharmaceutics*, vol. 60, pp. 191-196 (1990).

Davis, "Formulation strategies for absorption windows", *Drug Discovery Today*, vol. 10, No. 4, pp. 249-257 (2005).

AT Ortho Pharmaceutical Corp., "P-K Liquid-Solids Blender Granulates Tablet Formulations in a Single Step, Pre-Blends, Disperses, Granulates", *Industrial Engineering and Chemistry, Patterson and Kelley, Chemical and Process Equipment Division*, vol. 53, No. 4, pp. 40A-41A (Apr. 1961).

Lieberman et al., editors, *Pharmaceutical Dosage Forms—Tablets*, 2nd ed., rev. and expanded, Marcel Dekker, Inc., New York, USA, vols. 1-3, 17 pages (1989) Title pages and Tablets of Contents.

Ashford, "Gastrointestinal tract—physiology and drug absorption", *Aulton's pharmaceuticals: The design and manufacture of medicines, Third Edition*, Aulton, Ed., Churchill Livingstone Elsevier, Elsevier Limited, Chapter 20, pp. 270-278 (2007).

Berner et al., "Case studies in swelling polymeric gastric retentive tablets", *Expert Opin. Drug Deliv.*, vol. 3, No. 4, pp. 541-548 (2006).

Glumetza (metformin hydrochloride extended-release tablets), *Highlights of Prescribing Information*, 10 pages (2011).

Gralise (gabapentin), *Highlights of Prescribing Information*, 24 pages (2012).

Prinderre et al., "Advances in gastro retentive drug-delivery systems", *Expert Opin. Drug. Deliv.*, vol. 8, No. 9, pp. 1189-1203 (2011).

* cited by examiner

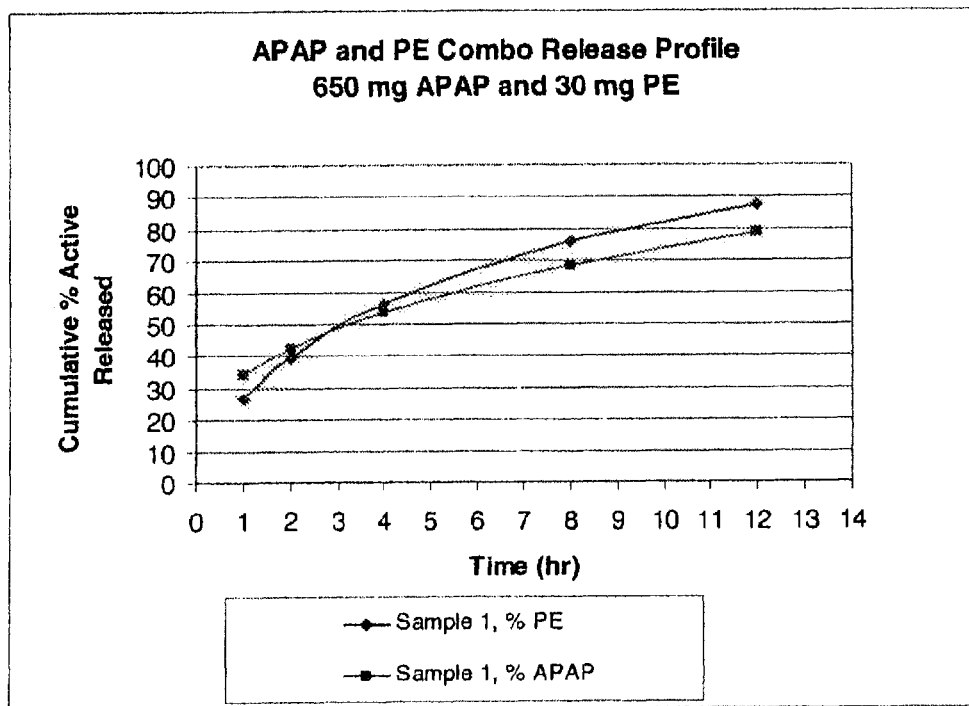


FIG. 1

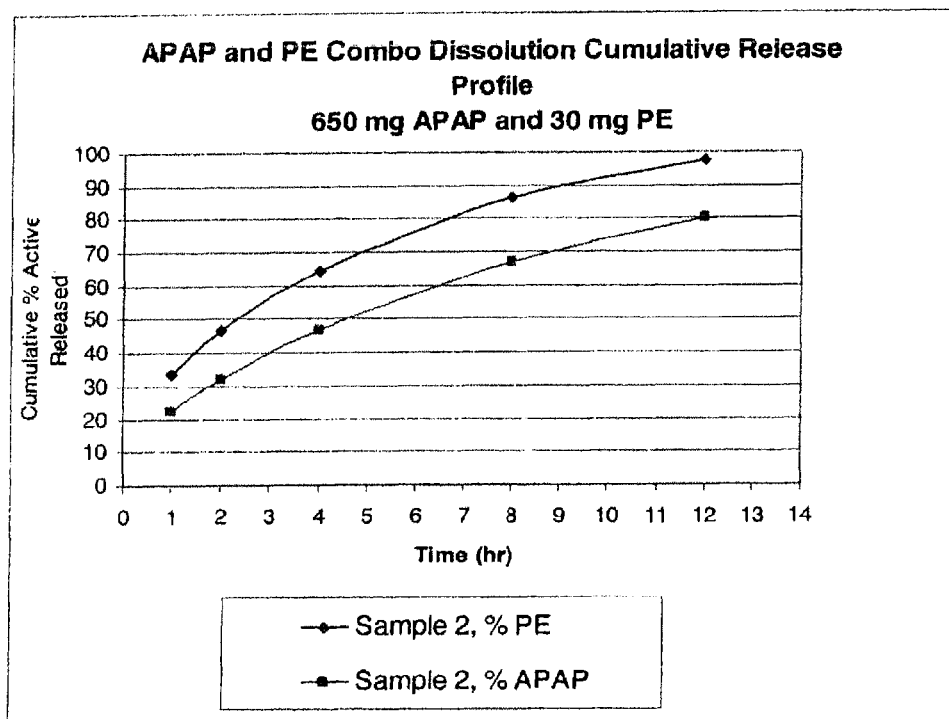


FIG. 2

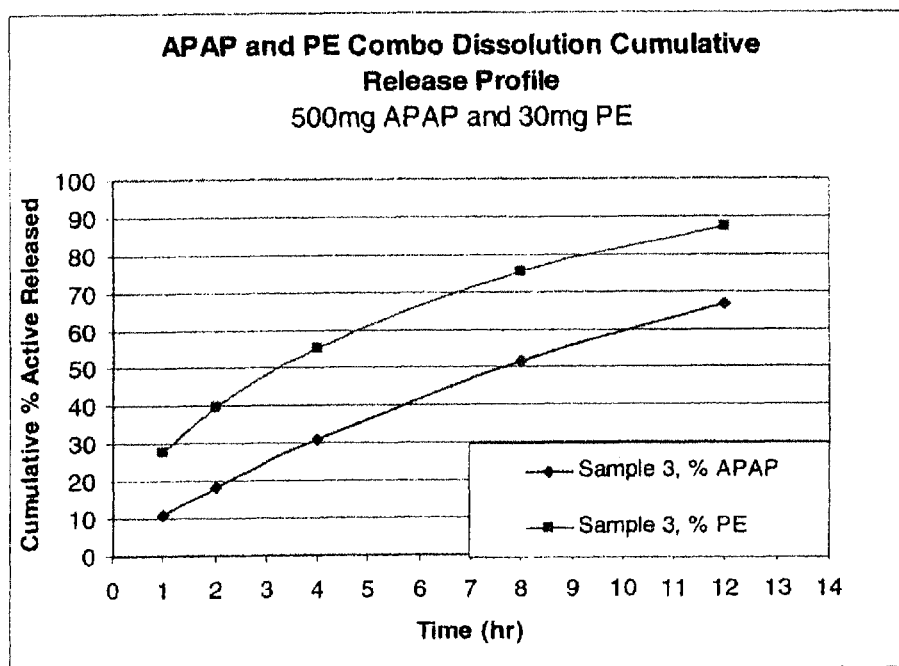


FIG. 3

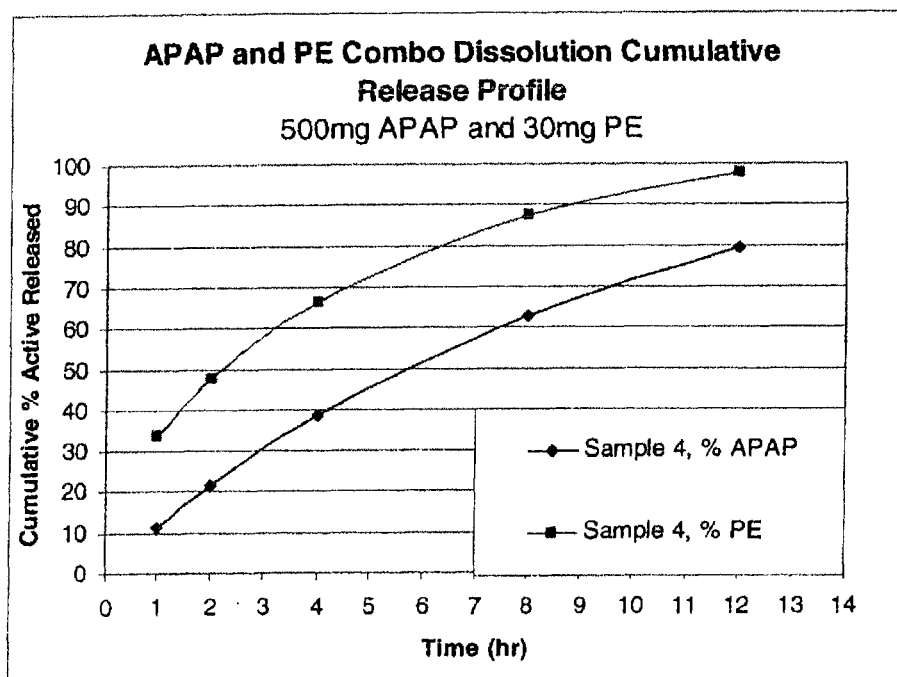


FIG. 4

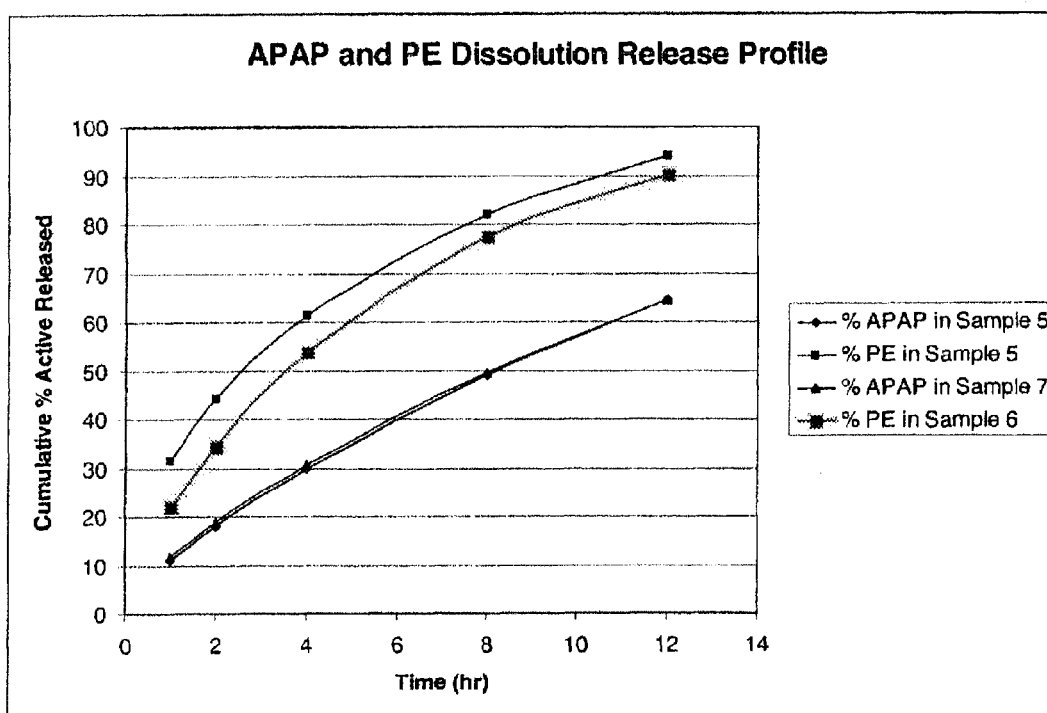


FIG. 5

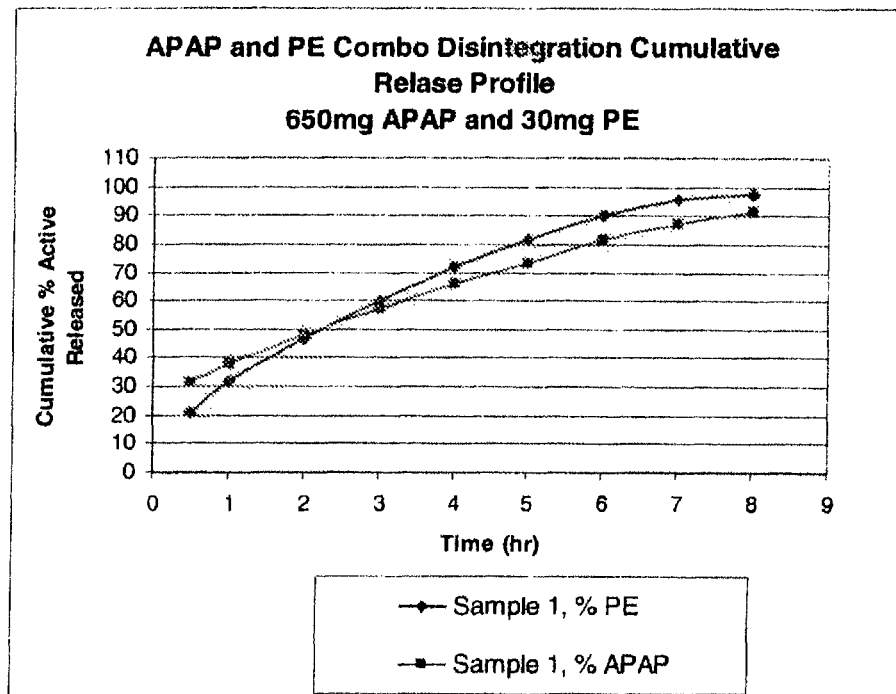


FIG. 6

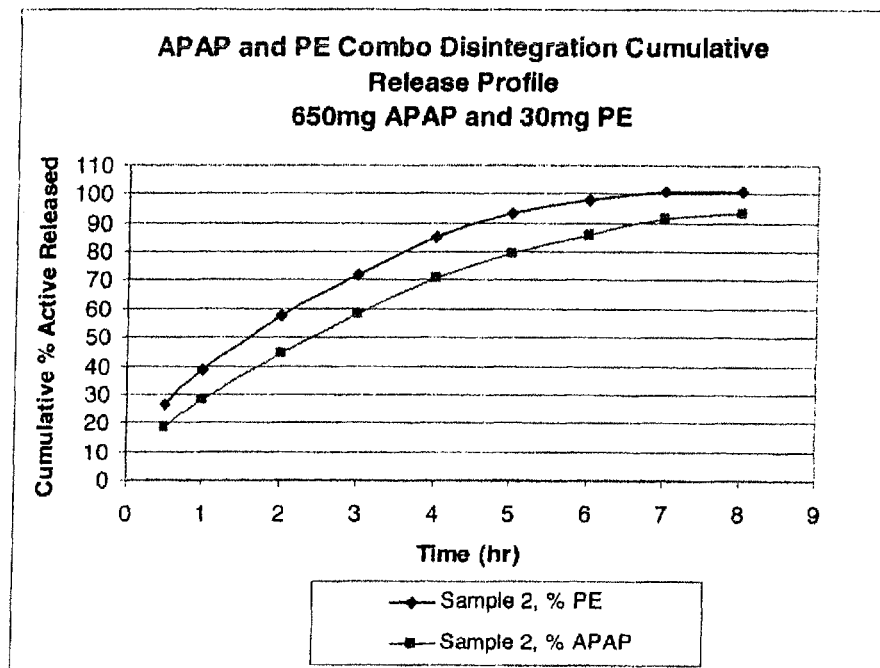


FIG. 7

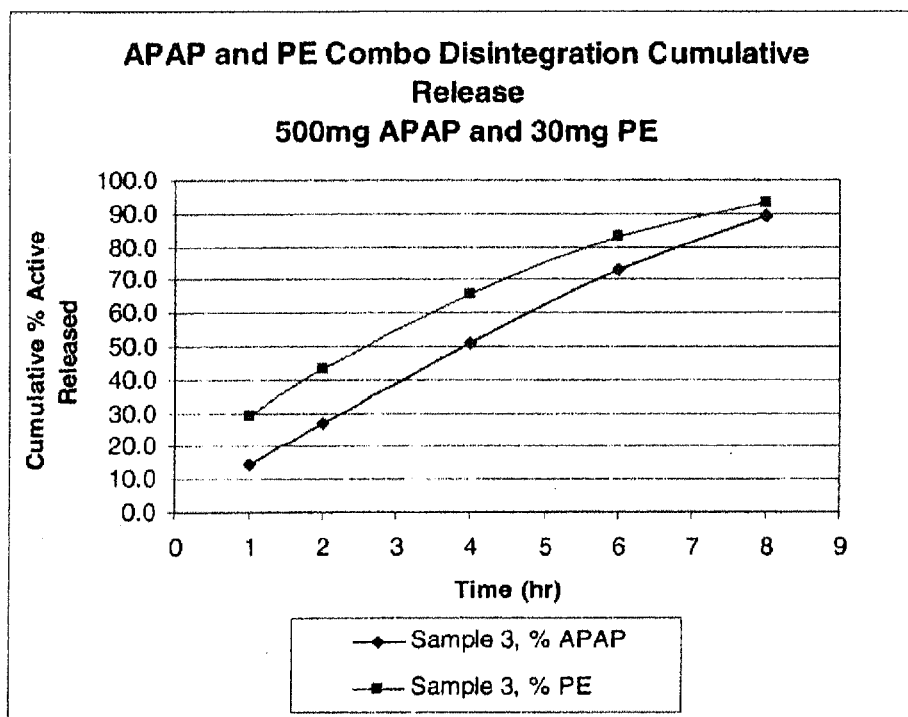


FIG. 8

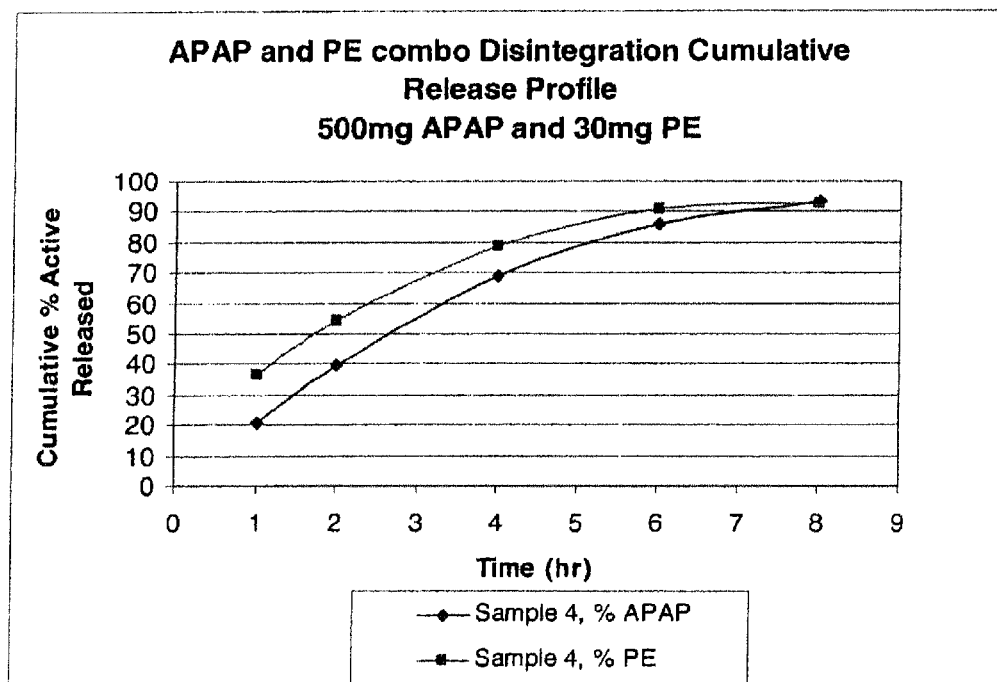


FIG. 9

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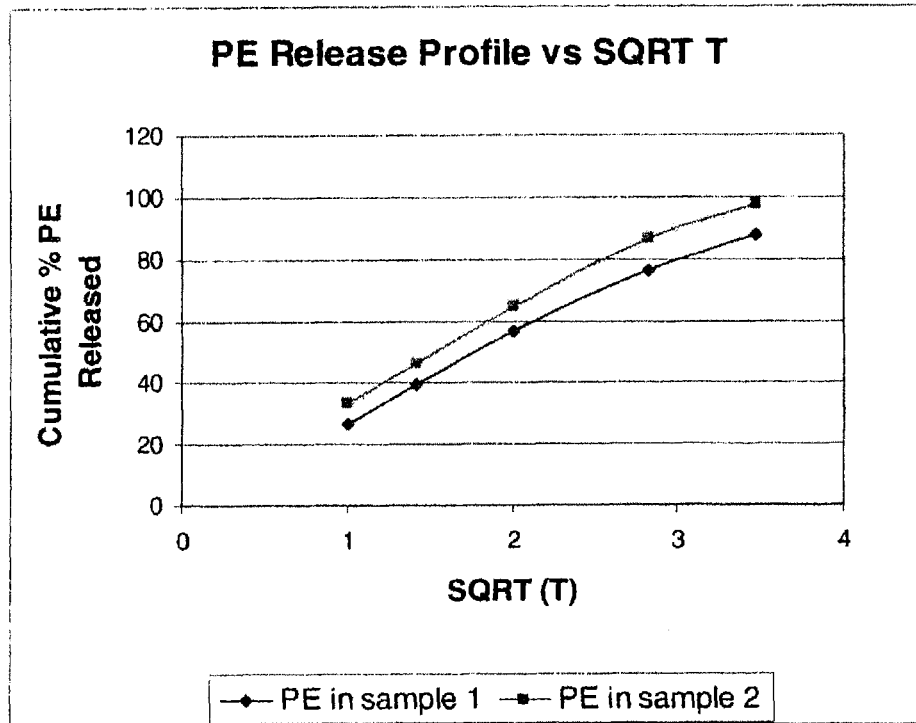


FIG. 10

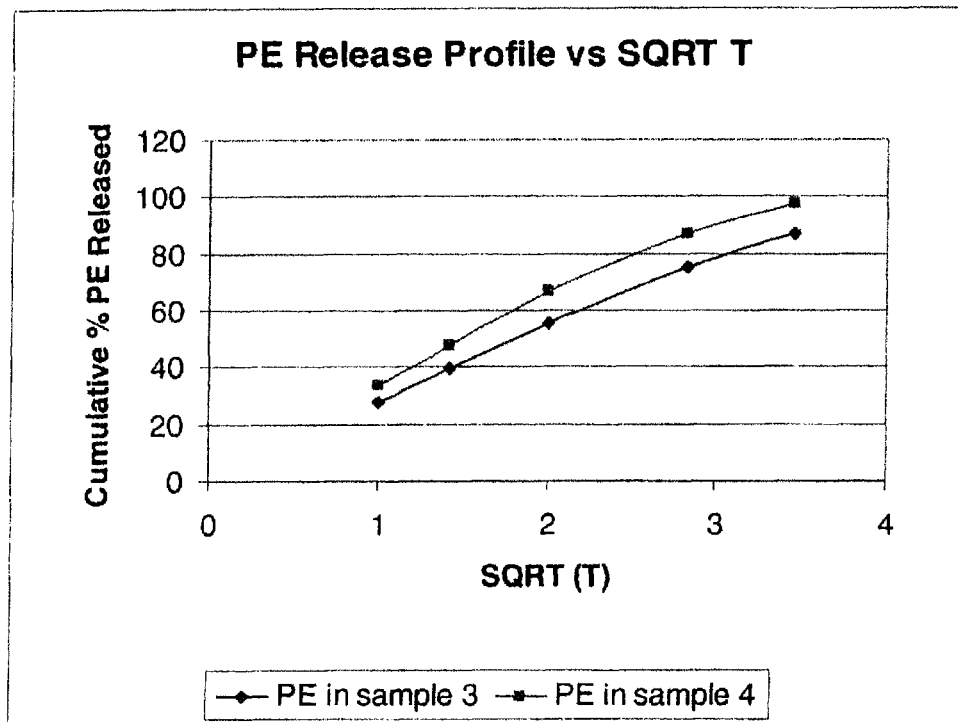


FIG. 11

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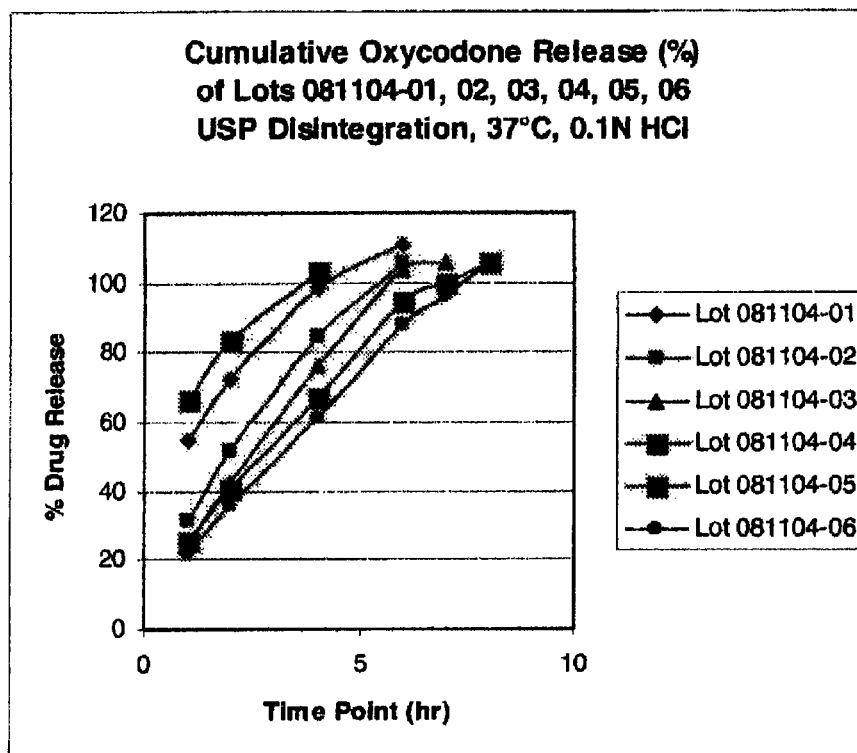


FIG. 12

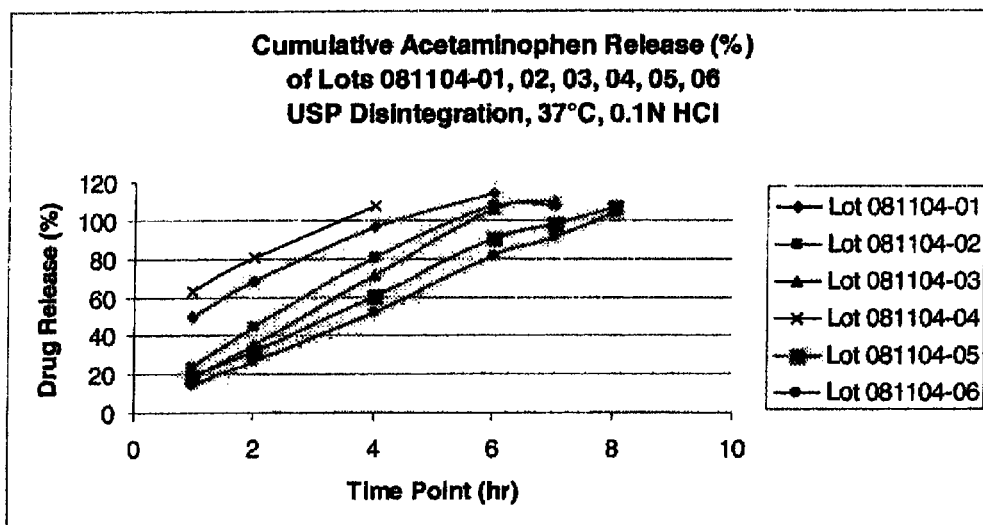


FIG. 13

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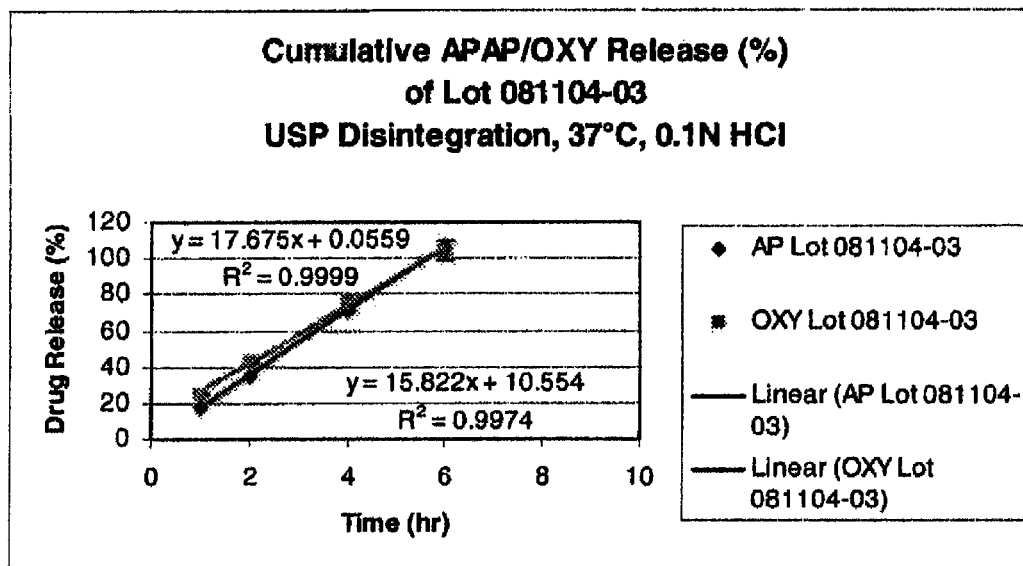


FIG. 14

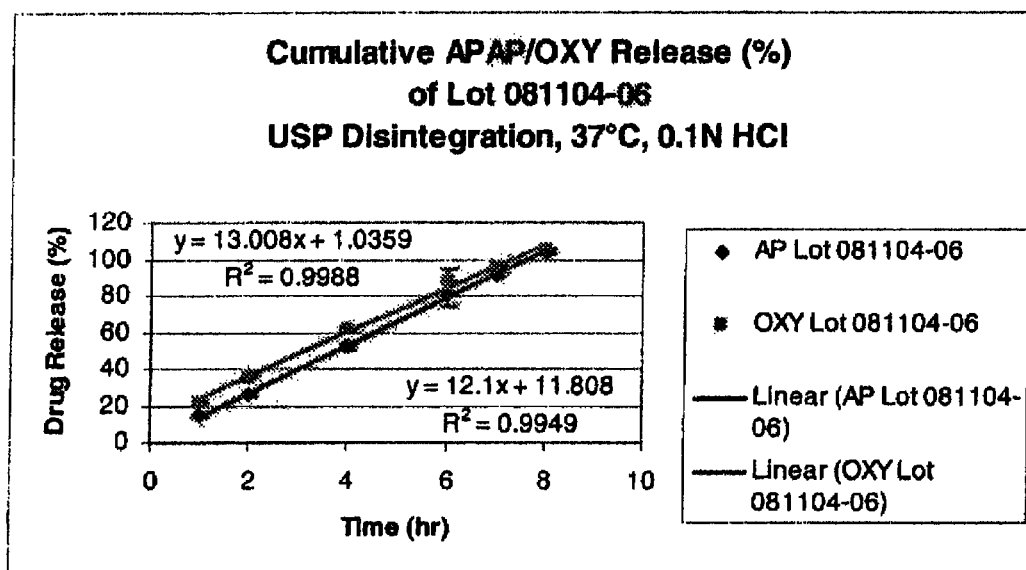


FIG. 15

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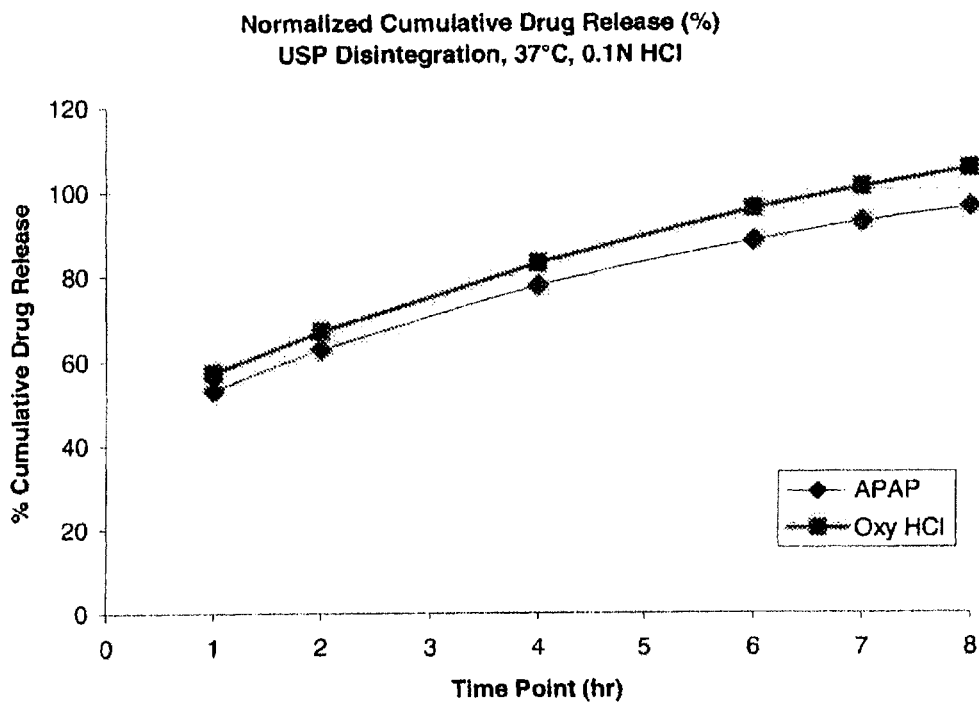


FIG. 16

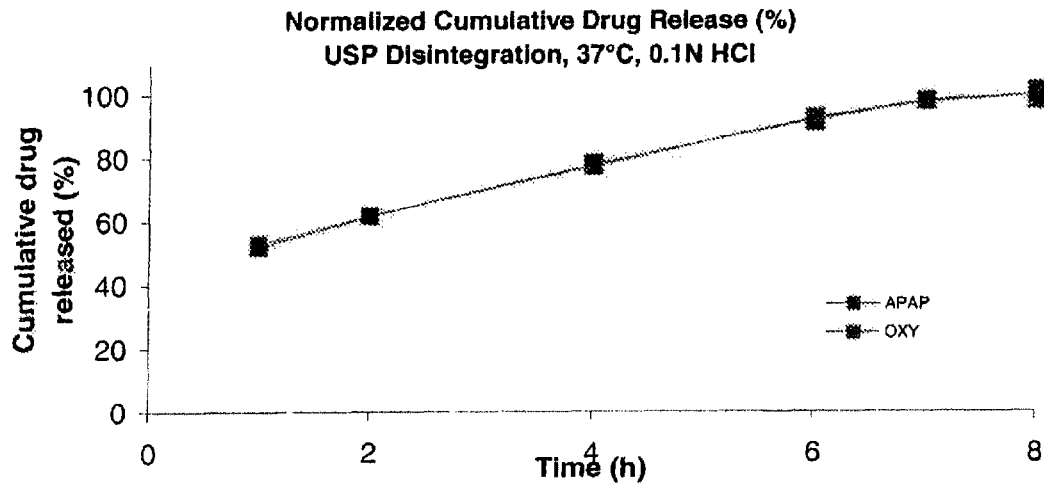


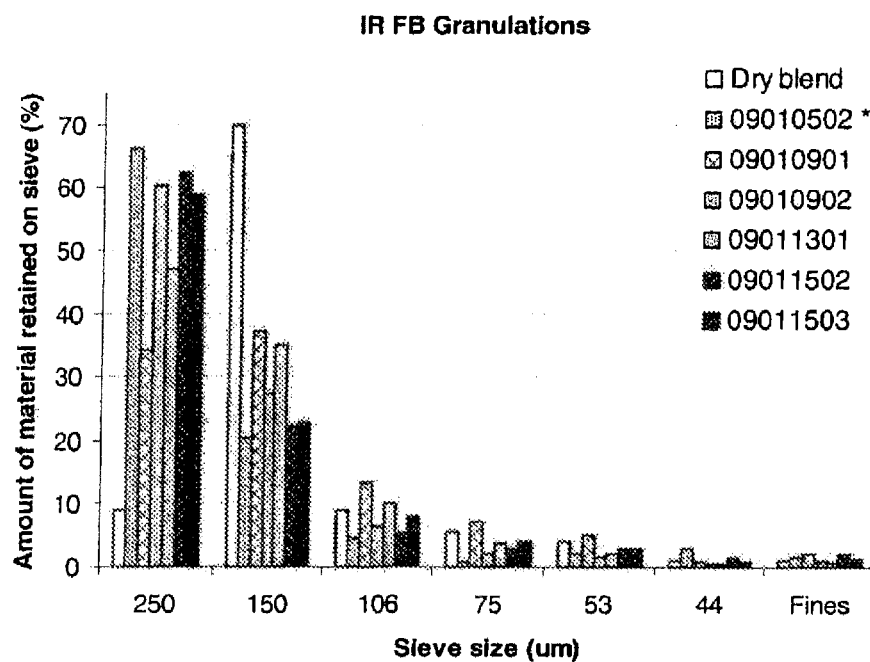
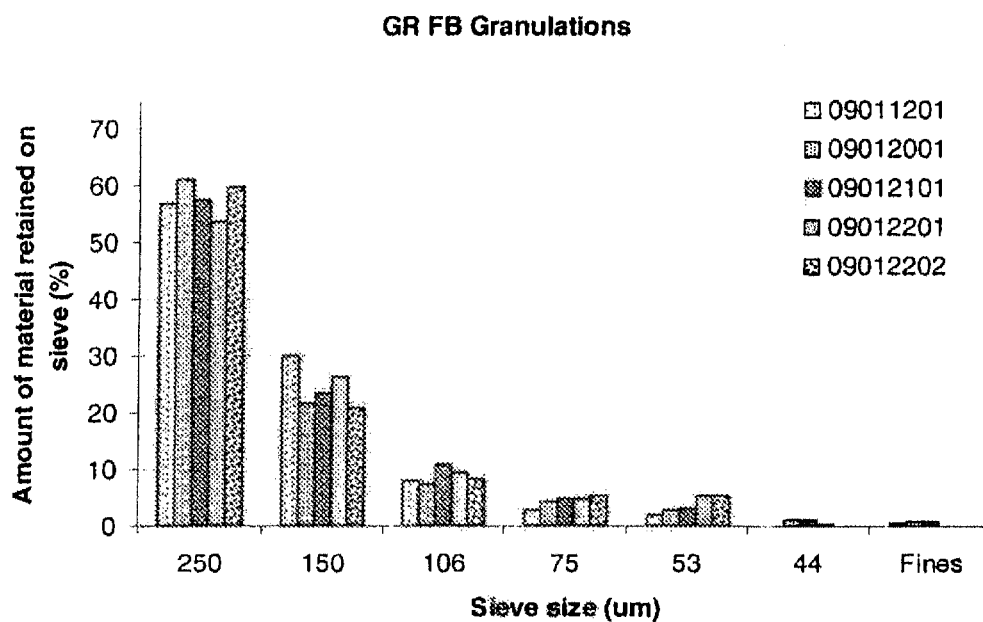
FIG. 17

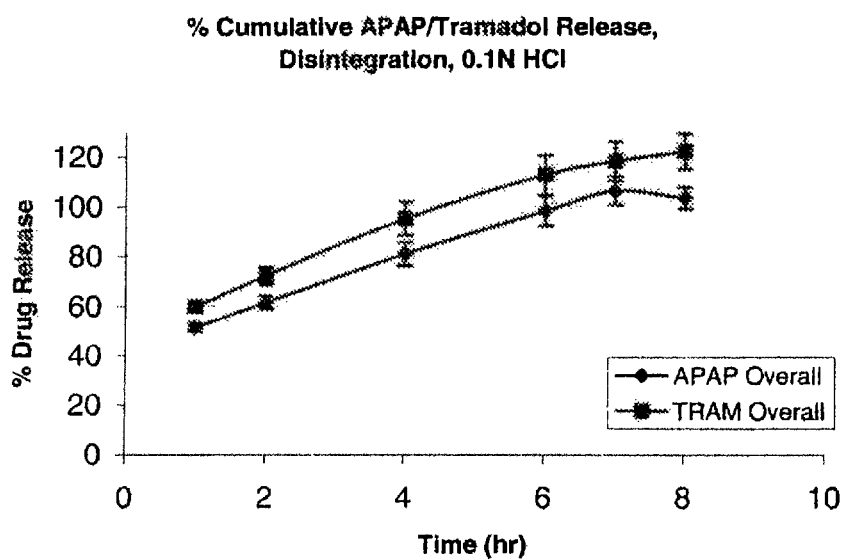
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**FIG. 20**

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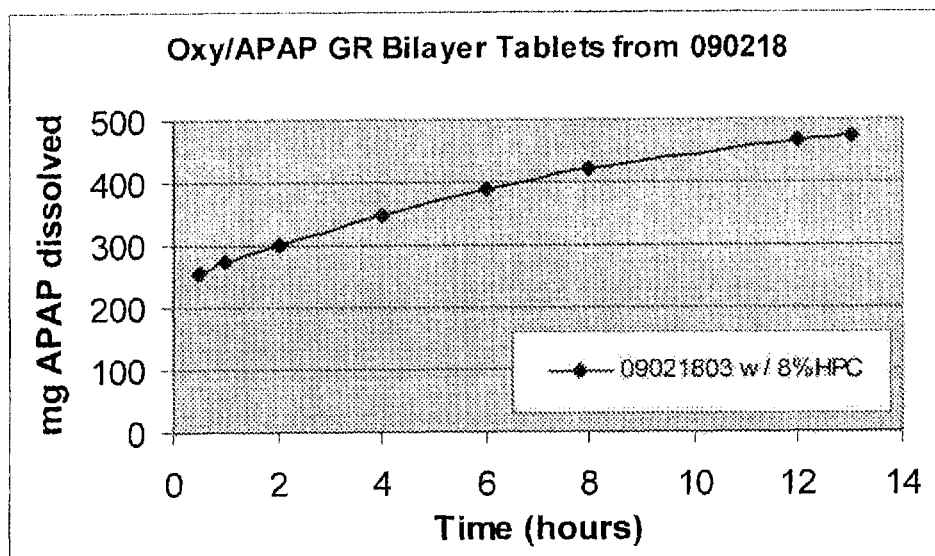


FIG. 21

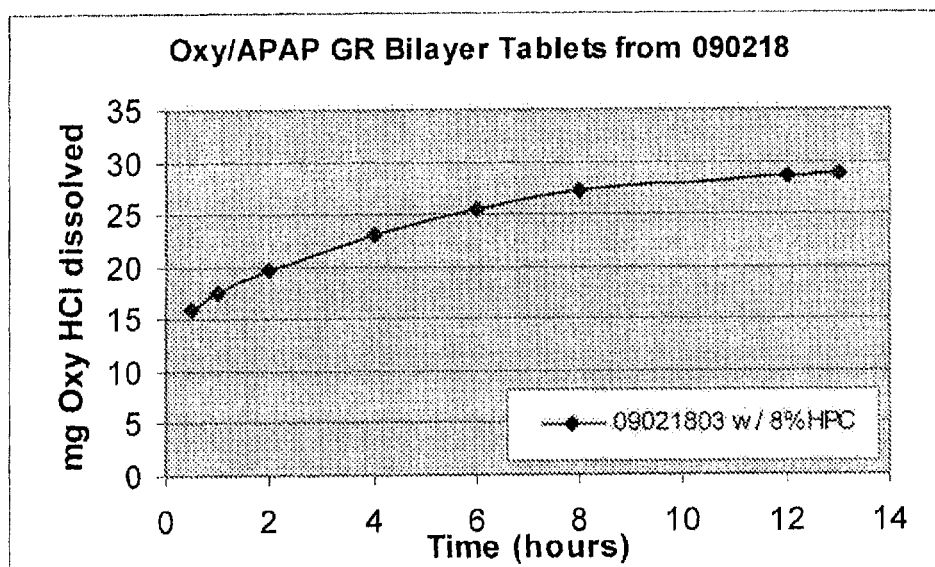
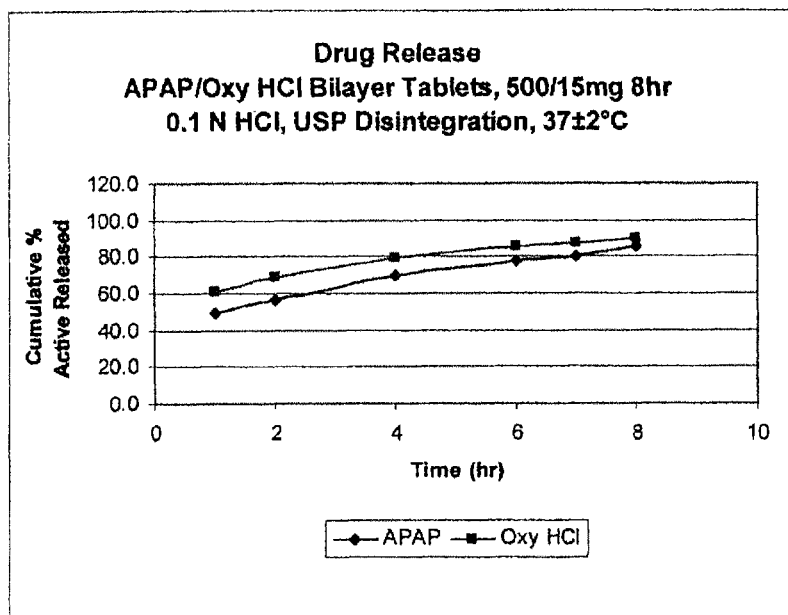
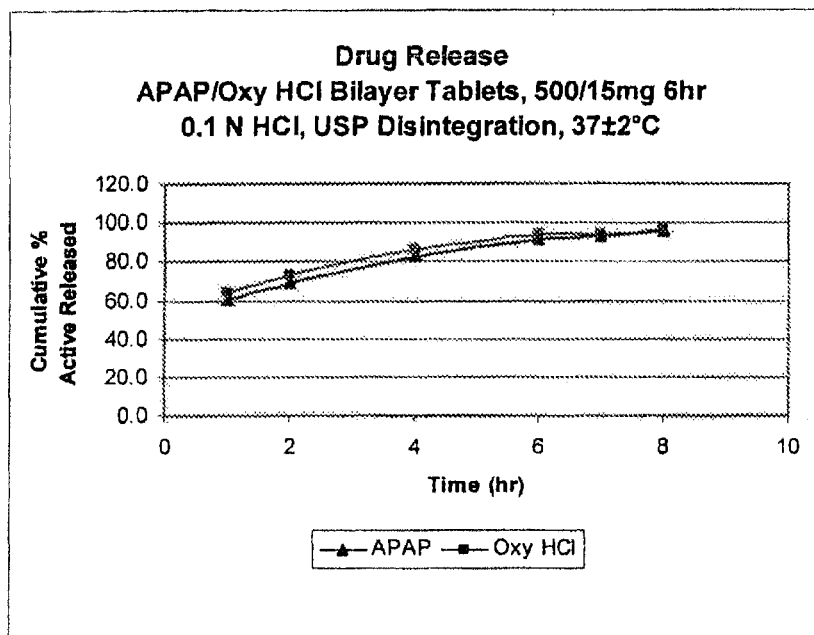
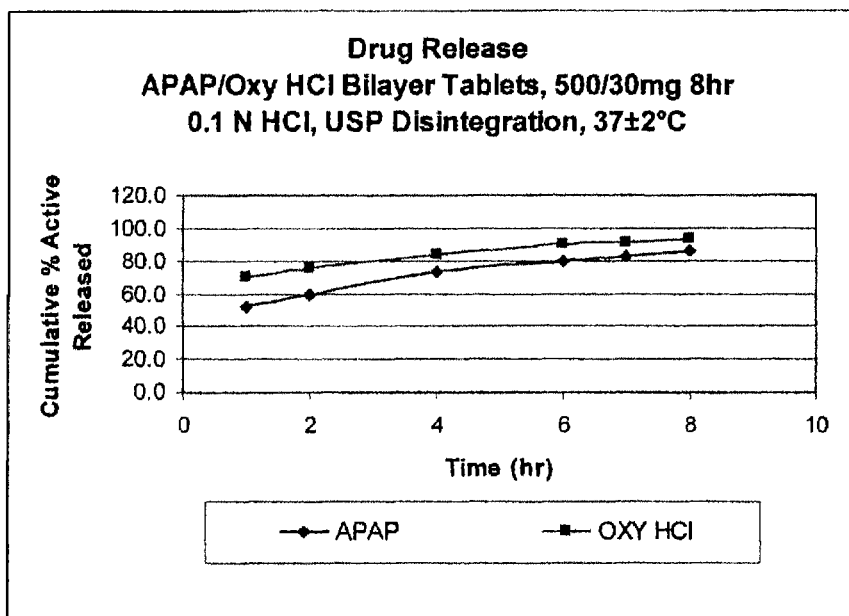
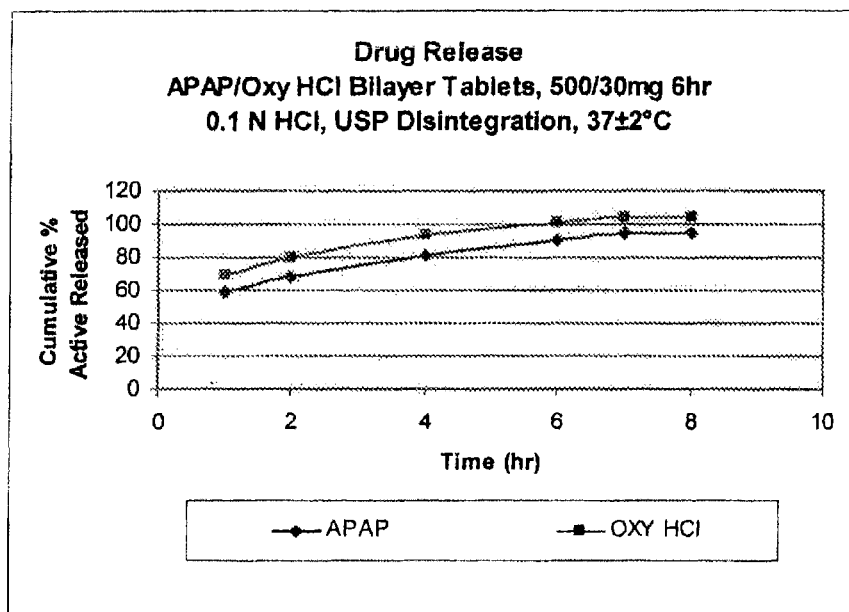
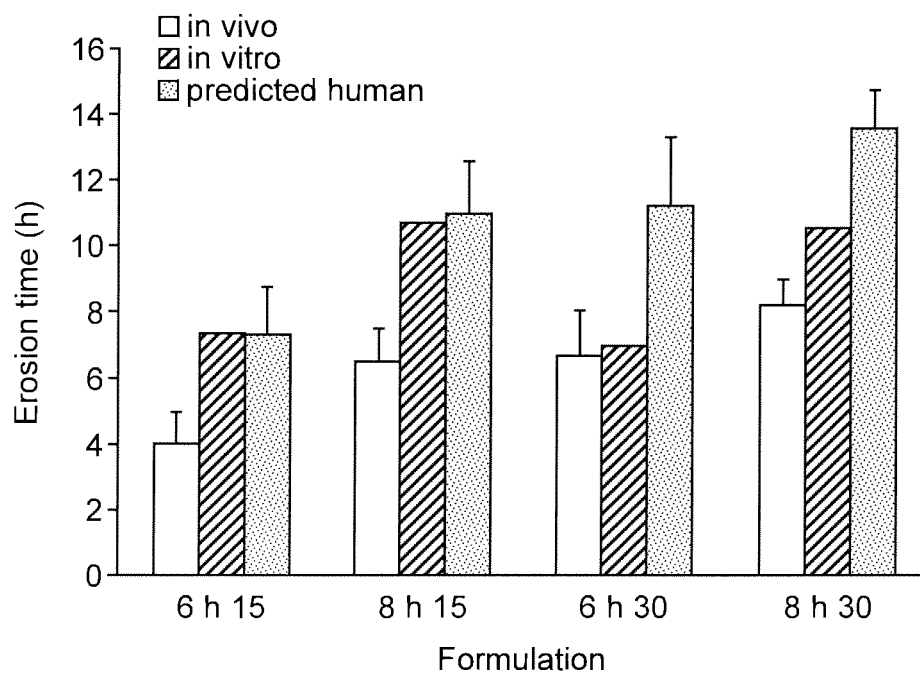


FIG. 22

**FIG. 23****FIG. 24**

**FIG. 25****FIG. 26**

**Fig. 27**

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**GASTRIC RETENTIVE
EXTENDED-RELEASE DOSAGE FORMS
COMPRISING COMBINATIONS OF A
NON-OPIOID ANALGESIC AND AN OPIOID
ANALGESIC**

This application is a continuation of U.S. application Ser. No. 12/644,444, now issued U.S. Pat. No. 8,372,432, filed Dec. 22, 2009 which is a continuation-in-part of U.S. application Ser. No. 12/402,477, now issued U.S. Pat. No. 8,377,453, filed Mar. 11, 2009, which claims the benefit of U.S. Provisional Application No. 61/035,696 filed Mar. 11, 2008, all of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

Compositions and methods are described for relief or treatment of existing or anticipated pain. In some embodiments, gastric retentive ("GR") dosage forms comprise acetaminophen (APAP) in combination with an opioid analgesic and are administered to a person suffering from, diagnosed with or at risk of experiencing pain. The dosage forms when administered to a mammal, typically provide about 3 hours to about 12 hours of delivery of one or both of the drugs to the upper gastrointestinal ("GI") of the mammal. The present disclosure also relates to a method for treating pain by providing the gastric retentive dosage forms, and to methods of making the gastric retentive dosage forms.

BACKGROUND

It is often desirable to administer to a mammalian subject an opioid analgesic combined with a non-opioid analgesic agent, for example, acetaminophen (APAP). Such combination formulations provide the advantage of additive analgesic effects with a lower dose of opioid, and hence a resulting lower incidence of side effects and the ability to treat a broader spectrum of pain or pain states due to different mechanisms of actions.

Such is the case for combinations of acetaminophen or aspirin with opioids, such as oxycodone (Percocet® and Percodan®, respectively), or hydrocodone (Vicodin® and Lortab®, respectively) or acetaminophen with codeine (Tylenol® with codeine). However, these currently marketed drug products deliver the combination drugs as an immediate release product. Accordingly, the drug product has to be administered quite frequently and at least every 4 to 6. Currently, extended-release oral dosage forms for delivery of the above active ingredients are only available for delivery of a single active pharmaceutical ingredient. For example, Tylenol® Extended Release for Arthritis provides a dosage of 650 milligrams acetaminophen to be administered every 8 hours. OxyContin® is formulated to provide controlled release of oxycodone hydrochloride via twice-daily administration.

When treating a mammalian subject suffering from or diagnosed with a chronic or acute pain state, it is highly desirable to maintain and achieve analgesia continuously. Immediate release formulations of the appropriate therapeutic agents require frequent and/or continuous dosing throughout the day (or night) for continuous pain relief. This is often inconvenient and difficult to maintain regularly dosing and frequently leads to poor patient compliance, potentially resulting in a dose being taken after pain breaks through again, causing unnecessary pain and suffering.

Hence, it would be desirable and beneficial to provide extended release delivery of a drug product that comprises

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both an opioid and a non-opioid analgesic such as acetaminophen. Such a dosage form would reduce the frequency of administration to a subject while sustaining plasma drug levels and analgesic effects throughout the day (or night). Such an extended release dosage form would eliminate the need to dose frequently to maintain analgesia, which is often inconvenient and difficult to maintain regularly, with the result that the next dose is taken after the pain breaks through again, causing unnecessary pain and suffering. Additionally, such a dosage form would increase patient compliance while minimizing adverse effects or events.

Gastric retentive dosage forms have demonstrated success in providing extended delivery of active ingredients. Drugs that are delivered from a gastric retained dosage form continuously bathe the stomach, duodenum and upper part of the small intestine for many hours. Release of the drug from the dosage form upstream of absorption sites provides extended and controlled exposure of the absorption sites to the released drug, thus increasing bioavailability. Acetaminophen demonstrates reduced bioavailability when administered rectally (about 35-50%) as compared to oral administration (about 60-70%). The increasingly dry environment of the colon is unfavorable for absorption. Accordingly, a gastric retentive extended release dosage form would provide several significant advantages as it would obviate the bioavailability reduction seen in the colon with non-gastric retentive extended release dosage forms.

Although gastric retentive dosage forms containing a drug dispersed in a swellable polymer matrix have been previously described, new challenges arise when formulating dosage forms that can provide the therapeutically effective delivery of a combination of drugs, which include, for example, acetaminophen and an opioid. Firstly, these two active agents have very different solubilities. Acetaminophen is a sparingly soluble drug in water, having a solubility of about 1-5 milligrams/milliliter (mg/ml) in water at 22° C. In contrast, opioids, which are formulated as acid salts in drug products, are highly soluble in water. For example, oxycodone HCl (100 to 167 (mg/ml), hydrocodone bitartrate (62.5 mg/ml), and codeine phosphate (400 to 435 mg/ml). Such disparities in solubility should be taken into account when formulating a dosage form that releases the two active agents at rates proportional to each other. Secondly, opioids are known to inhibit gastric motility. Such inhibition can negatively impact the erosion rate of a gastric retentive dosage form as needed for the desired drug release profile. Finally, acetaminophen is known to be difficult for the production of solid oral dosage forms. It can be particularly difficult to produce a tablet having acetaminophen because acetaminophen powder does not compress easily to form a stable tablet. Moreover, preparation of tablets having necessary dosage levels requires a relatively high weight percent of the drug. As a result, production of a useful tablet size allows only low amounts of excipients. This contributes to the difficulties involved in producing a tablet that relies on the use of a swellable polymer for extended release.

The present disclosure meets these challenges and needs, among others.

SUMMARY

The present disclosure provides, among other aspects, gastric retentive dosage forms for oral administration to a subject, such as a human patient, for relief from a pain state. The dosage form in some embodiments is a gastric retentive dosage form that contains a first dose of at least one drug as an extended release ("ER") portion, and a second dose of at least

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one drug as an immediate release ("IR") component. The dosage forms typically contain a therapeutically effective amount of acetaminophen (APAP) and a therapeutically effective amount of an opioid or opioid-like analgesic.

In one aspect, the ER portion of the dosage form comprises an opioid and acetaminophen containing a first dose of the opioid and a first dose of acetaminophen. In another aspect, the ER portion of the dosage form comprises the first dose of opioid and the first dose of acetaminophen dispersed in a polymer matrix comprising at least one hydrophilic polymer. Upon administration, the polymer matrix is able to swell upon imbibition of fluid to a size sufficient such that the ER portion of the dosage form is retained in a stomach of a subject in a fed mode and the first dose of opioid and the first dose of acetaminophen are released over an extended period of time. The ER portion may alternatively be referred to herein as the gastric retentive or "GR" portion.

In another aspect, the dosage form releases the acetaminophen through erosion of the polymer matrix and the opioid is released at a rate proportional to the release of the acetaminophen. In another embodiment, the dosage form releases the acetaminophen through both erosion and diffusion. In additional embodiments, the rate of release of the opioid is about 2% to about 10%, or about 4% to about 8%, or about 5% or about 7% of the rate of release of the acetaminophen, over a period of release from between about 2 to about 10 hours, or about 4 to about 6 hours, or about 4 to about 8 hours.

In one embodiment, the opioid or opioid-like analgesic is tramadol, hydrocodone, oxycodone, hydromorphone or codeine.

In one embodiment, the ER portion of the dosage form comprises a first dose of acetaminophen of about 100 milligrams (mg) to about 600 mg and is delivered over an extended period of time. In another embodiment, the first dose of acetaminophen is about 200 mg to about 400 mg, or about 275 mg to about 325 mg. In yet another embodiment, the first dose of acetaminophen is about 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, 300 mg, 304 mg, 305 mg, 310 mg, 315 mg, 320 mg, 325 mg or 330 mg. In another aspect, the ER portion of the dosage form comprises a first dose of acetaminophen that is approximately 25 weight percent (wt %), 30 wt %, 35 wt %, 38 wt %, 39 wt %, 40 wt %, 41 wt %, 42 wt %, 43 wt %, 44 wt %, 45 wt %, 47 wt %, 50 wt %, 55 wt %, 60 wt %, 65 wt % or 70 wt % of the total weight of the dosage form.

In one embodiment, the ER portion of the dosage form comprises a first dose of opioid of about 10 mg to about 100 mg. In another embodiment, the first dose of opioid is about 14 mg to about 25 mg. In another embodiment, the first dose of opioid is about 15 mg to about 50 mg. In an additional embodiment, the first dose of opioid is about 16 mg to about 30 mg. In another embodiment, the first dose of opioid is about 16.5 mg to about 20 mg. In yet another embodiment, the first dose of opioid is about 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, or 20.0 mg. In yet another embodiment, the ER portion of the polymer matrix comprises a first dose of opioid that is approximately 1.0 wt %, 1.5 wt %, 2.0 wt %, 2.2 wt %, 2.5 wt %, 2.6 wt %, 2.7 wt %, 2.8 wt %, 3.0 wt %, 3.2 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt %, 8.0 wt %, 8.5 wt %, 9.0 M %, 9.5 wt % or 10 wt % of the total weight of the ER portion of the dosage form.

In another embodiment, the weight percent of acetaminophen is typically between about 10 to 20 times, more typically between 14 to 17 times the weight percent of opioid in the ER portion of the dosage form.

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In one embodiment, the at least one polymer is a polyalkylene oxide. In another aspect, the polyalkylene oxide is poly(ethylene) oxide. In a further embodiment, the poly(ethylene) oxide has an approximate molecular weight between 500,000 Daltons (Da) to about 10,000,000 Da or about 900,000 Da to about 7,000,000 Da. In yet a further embodiment, the poly(ethylene) oxide has a molecular weight of approximately 600,000 Da, 900,000 Da, 1,000,000 Da, 2,000,000 Da, 4,000,000 Da, 5,000,000 Da, 7,000,000 Da, 9,000,000 Da and 10,000,000 Da.

In another embodiment, the polymer is present in the ER portion of the dosage form from about 15 wt % to about 70 wt %, or about 20 wt % to about 60 wt %, or about 25 wt % to about 55 wt % of the total wt % of the dosage form of the ER portion. In another embodiment, the polymer is present in the ER portion of the dosage form in an amount ranging from about 30 wt % to about 50%, or about 35 wt % to about 45 wt %. In yet another embodiment, the polymer is present in the ER portion of the dosage form in an amount equal to approximately 30 wt %, 35 wt %, 40 wt %, 45 wt %, 50 wt %, 55 wt % or 60 wt % of the ER portion.

In one embodiment, the ER portion of the dosage form further comprises a binder. In another embodiment, the binder is selected from the group consisting of polyvinylpyrrolidone (povidone), a hydroxyalkylcellulose such as hydroxypropylcellulose, starches, pregelatinized starches, gelatin, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohols, polyethylene glycol, polyols. In another embodiment, the ER portion of the dosage form comprises a binder that is present in an amount that is about 2.0 wt %, 2.5 wt %, 3.0 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt % or 8.0 wt % of the ER portion.

In one embodiment, the ER portion of the dosage form further comprises a filler. In another embodiment, the filler is selected from microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, mannitol, sorbitol, and inorganic compounds. In another embodiment, the ER portion of the dosage form comprises a filler that is present in an amount that is about 1.0 wt %, 1.5 wt %, 2.0 wt %, 2.5 wt %, 3.0 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt %, 8.0 wt %, 8.5 wt %, 9.0 wt %, 9.5 wt % or 10 wt % of the ER portion of the dosage form.

In one embodiment, the ER portion of the dosage form further comprises a lubricant. In another embodiment, the lubricant is magnesium stearate. In another embodiment, the ER portion of the dosage form comprises a lubricant that is present in an amount that is about 0.1 wt %, 0.5 wt %, 0.75 wt %, 1.0 wt %, 1.5 wt %, 1.75 wt %, 1.80 wt %, 1.85 wt %, 1.90 wt % or 2.0 wt % of the ER portion.

In one embodiment, the ER portion of the dosage form comprises an anti-oxidant which is ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphatocopherol, or propylgallate. In another embodiment, the antioxidant is present in the ER portion of the dosage form at a wt % ranging from about 0.10 wt % to about 0.20 wt %, or from about 0.05 wt % to about 0.30 wt %.

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In yet another embodiment, the antioxidant is present in the ER portion of the dosage form at a wt % of about 0.01 wt %, 0.05 wt %, 0.10 wt %, 0.15 wt %, 0.20 wt %, 0.25 wt %, 0.35 wt %, 0.50 wt %, 0.75 wt %, 1.00 wt %, 2.00 wt %, 3.00 wt % or 4.00 wt % of the ER portion.

In one embodiment, the ER portion of the dosage form comprises a chelating agent. In another embodiment, the chelating agent is selected from ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetracetic acid, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetracetic acid, 1,4,7,10-tetraazacyclododecane-N,N',N''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetracetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicycysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N,N',N'-tetracetic acid. In a further embodiment, the chelating agent is the sodium salt of EDTA. In yet another embodiment, the ER portion of the dosage form comprises a chelating agent which is present in an amount that is about 0.01 wt % to about 0.10 wt % or about 0.02 to about 0.08 wt % of the ER portion. In yet another embodiment, the ER portion of the dosage form comprises a chelating agent which is present in an amount which is about 0.01 wt %, 0.02 wt %, 0.03 wt %, 0.04 wt %, 0.05 wt %, 0.06 wt %, 0.07 wt %, 0.08 wt %, 0.09 wt % or 0.10 wt %.

In one embodiment, the ER portion of the dosage form comprises a color agent. In another embodiment, the color agent is present in an amount that is about 2.0 wt % to about 5.0 wt % of the ER portion of the dosage form. In yet another embodiment, the color agent is present in an amount that is about 1.0 wt %, 1.5 wt %, 2.0 wt %, 2.5 wt %, 3.0 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, or 5.0 wt % of the ER portion.

In another embodiment, the ER portion of the dosage form comprises particles of acetaminophen admixed with the opioid and the polymer.

In one embodiment, the ER portion of the dosage form comprises particles wherein the particles have an average particle size greater than about 20 microns and less than about 2000 microns, greater than about 50 microns and less than about 1500 microns, greater than about 100 microns and less than about 1000 microns, greater than about 150 microns and less than about 1000 microns, or greater than about 200 microns and less than about 2000 microns.

In one embodiment, the ER portion of the dosage form comprises particles wherein at least about 50% of the particles are greater than about 250 microns in size. In another embodiment, about 20% to about 30% of the particles are greater than about 150 microns and less than about 250 microns.

In another embodiment, after oral administration to a subject, the opioid is released from ER portion of the dosage form at a rate proportional to release of the acetaminophen for a period of at least about 4 hours (h). In another embodiment, the proportional rate of release occurs for a period of at least about 5 h, 6 h, 7 h, or 8 h. In yet another embodiment, the first dose of opioid is released from the ER portion of the dosage form at a rate proportional to release of the first dose of acetaminophen for a period of about 4 h to about 8 h. In another embodiment, the proportional rate of release occurs over a period of about 5 h to about 6 h. In another embodiment, the ER portion of the dosage form comprises particles of acetaminophen admixed with the opioid and the polymer.

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In some embodiments, the ER portion of the dosage form swells upon administration to a size that is about 110% to about 160%, or about 120% to about 150%, or about 125% to about 145%, or about 130% to about 145% of the size of the dosage form within 30 minutes of administration. In other embodiments, the ER portion of the dosage form swells to a size that is approximately 130% of the size of the dosage form within 30 minutes of administration.

In another embodiment, upon administering of the dosage form to a subject, the dosage form provides at least about 4 hours to about 12 hours of drug delivery to the upper gastrointestinal tract, which includes the stomach and the small intestine. In another embodiment, the dosage form provides at least 6 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the dosage form provides at least 8 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the dosage form provides at least 9 hours, 10 hours, 11 hours or 12 hours of drug delivery to the upper gastrointestinal tract.

In some embodiments, the dosage form provides a dissolution profile wherein for each of the first dose of acetaminophen and the first dose of the opioid, between about 40% to about 50% of the first dose remains in the dosage form between about 1 and 2 hours after administration. In one embodiment, not more than 50% of the first dose of acetaminophen and first dose of opioid is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the first dose of acetaminophen and first dose of opioid is released within about the first hour. In another embodiment, not more than 85% of the first dose of acetaminophen and first dose of opioid is released within about 4 hours. In another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 60% is released after about 6 hours.

In one embodiment, the dosage form further comprises an IR portion. The IR portion of the dosage form typically comprises a second dose of an opioid and a second dose of acetaminophen. In another embodiment, the opioid and the acetaminophen are dispersed in the IR portion of the dosage form. In yet another embodiment, a dosage form comprising an IR portion in contact with an ER portion is provided.

In one embodiment, the IR portion of the dosage form comprises about 50 mg to about 900 mg, about 75 mg to about 700 mg, about 100 mg to about 600 mg, or about 150 mg to about 250 mg of acetaminophen. In yet another embodiment, the IR portion of the dosage form comprises about 200 mg to about 400 mg of acetaminophen. In yet another embodiment, the IR portion of the dosage form comprises about 180 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg or 235 mg of acetaminophen.

In another embodiment, the IR portion of the dosage form comprises about 5 mg to about 60 mg, or about 10 mg to about 40 mg, or about 15 mg to about 20 mg of the opioid. In yet another embodiment, the IR portion of the dosage form comprises about 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, or 17.0 mg of the opioid.

In another embodiment, the amount of acetaminophen in the IR portion is typically between about 10 to about 20, more typically between about 12 to about 16 times the amount of opioid in the IR portion. In another embodiment, the ratio of acetaminophen to opioid in the IR portion is about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

In yet another embodiment, the IR portion of the dosage form further comprises a binder. In some embodiments, the binder is selected from the group consisting of polyvinylpyrrolidone (povidone), hydroxypropylmethylcellulose (HPMC), polyvinyl alcohol, hydroxyethylcellulose, hydrox-

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ypropylcellulose, methylcellulose, methacrylic acid copolymers, ethylacrylate-methylmethacrylate copolymers, guar gum, arabic gum, xanthan gum, gelatine, pectin and mixtures thereof. In another embodiment, the binder is present in the IR portion of the dosage form in an amount that is about 4.5 wt %

In one embodiment, the IR portion of the dosage form comprises an anti-oxidant which is ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, or propylgallate. In another embodiment, the antioxidant is present in the IR portion of the dosage form at a wt % ranging from about 0.10 wt % to about 0.40 wt %, or from about 0.05 wt % to about 0.35 wt %. In yet another embodiment, the antioxidant is present in the IR portion of the dosage form at a wt % of about 0.01 wt %, 0.05 wt %, 0.10 wt %, 0.15 wt %, 0.20 wt %, 0.25 wt %, 0.30 wt %, 0.35 wt %, 0.50 wt %, 0.75 wt %, 1.00 wt %, 2.00 wt %, 3.00 wt % or 4.00 wt % of the IR portion.

In one embodiment, the IR portion of the dosage form comprises a chelating agent. In another embodiment, the chelating agent is selected from ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetraacetic acid, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraazacyclododecane-N,N',N''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicycysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N'',N'-tetraacetic acid. In yet another embodiment, the IR portion of the dosage form comprises a chelating agent which is present in an amount that is about 0.01 wt % to about 0.10 wt % or about 0.02 to about 0.08 wt % of the IR portion. In yet another embodiment, the IR portion of the dosage form comprises a chelating agent which is present in an amount which is about 0.01 wt %, 0.02 wt %, 0.03 wt %, 0.04 wt %, 0.05 wt %, 0.06 wt %, 0.07 wt %, 0.08 wt %, 0.09 wt % or 0.10 wt %.

In one embodiment, the IR portion of the dosage form comprises particles of acetaminophen granulated with the opioid and the binder.

In one embodiment, the IR portion of the dosage form comprises particles wherein the particles have an average particle size greater than about 20 microns and less than about 2000 microns, greater than about 50 microns and less than about 1500 microns, greater than about 100 microns and less than about 1000 microns, greater than about 150 microns and less than about 1000 microns, or greater than about 200 microns and less than about 2000 microns.

In one embodiment, the ER portion of the dosage form comprises particles wherein at least about 50% of the particles are greater than about 250 microns in size. In another embodiment, about 20% to about 30% of the particles are greater than about 150 microns and less than about 250 microns.

In one embodiment, the IR portion of the dosage form comprises particles, wherein at least 30% of the particles have a size greater than 250 microns (μ).

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In one embodiment, the dosage form is a pharmaceutical tablet, such as a gastric retentive tablet for the extended release of the opioid and the acetaminophen. In another embodiment, the tablet is a monolithic tablet comprising an ER portion. In another embodiment, the tablet is a monolithic tablet comprising an ER portion and an IR portion. In another embodiment, the tablet is a bilayer tablet, comprising an ER portion and an IR portion. The bilayer tablet is typically a monolithic tablet. In another embodiment, the dosage form is a capsule comprising an ER portion. In another embodiment, the dosage form is a capsule comprising ER portion and an IR portion.

In one embodiment, the bilayer tablet has a friability of no greater than about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.7% or 1.0%. In another embodiment, the bilayer tablet has a friability of greater than 0 but less than about 1.0%, greater than 0 but less than about 0.5%, greater than 0 but less than about 0.3%, or greater than 0 but less than about 0.2%.

In one embodiment, the bilayer tablet has a hardness of at least about 10 kilopond (also known as kilopons) (kp). In some embodiments, the tablet has a hardness of about 9 kp to about 25 kp, or about 12 kp to about 20 kp. In further embodiments, the tablet has a hardness of about 11 kp, 12 kp, 13 kp, 14 kp, 15 kp, or 16 kp.

In one embodiment, the tablets have a content uniformity of from about 85 to about 115 percent by weight or from about 90 to about 110 percent by weight, or from about 95 to about 105 percent by weight. In other embodiments, the content uniformity has a relative standard deviation (RSD) equal to or less than about 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1.0% or 0.5%.

In one embodiment, the dosage form comprises an opioid or an opioid-like compound chosen from: adulmine, alfentanil, allocryptopine, allylprodine, alphaprodine, anileridine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bezitramide, buprenorphine, bulbocaprine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacilmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papavereturn, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, and pharmaceutical salts of any of the foregoing.

In one embodiment, acetaminophen can be present in the dosage form in an amount ranging from about 100 milligrams (mg) to about 1300 mg.

In another embodiment, acetaminophen is present in the dosage form at an amount of about 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 400 mg, 425 mg, 450 mg, 500 mg, 525 mg, 530 mg, 535 mg, 540 mg, 545 mg, 550 mg, 600 mg, 650 mg or about 700 mg.

In some embodiments, an opioid is present in the dosage form at an amount of about 5 mg, 7.5 mg, 10 mg, 12 mg, 15 mg, 20 mg, 22.5 mg, 25 mg, 30 mg, 32 mg, 34 mg, 35 mg, 37 mg, 40 mg, 50 mg, 60 mg, 70 mg or higher. In one embodiment, wherein the opioid is tramadol, an amount of about 5 mg to about 40 mg, about 10 mg to about 30 mg, or about 15 mg to about 20 mg may be employed. In another embodiment, wherein the opioid is codeine, an amount of about 50 mg to

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about 300 mg, or about 75 mg to about 200 mg, or about 120 mg to about 180 mg may be employed. In yet another embodiment, wherein the opioid is oxycodone, an amount of 2 mg to about 100 mg, 5 mg to about 75 mg, about 5 mg to about 40 mg, about 10 mg to about 30 mg, or about 15 mg may be employed. In yet another embodiment, wherein the opioid is hydrocodone, an amount of 2 mg to about 80 mg, 5 mg to about 40 mg, about 10 mg to about 30 mg, or about 15 to about 20 mg may be employed.

In another aspect, a pharmaceutical or gastric retentive oral dosage form comprising acetaminophen and an opioid, wherein the formulation is administered to a mammal once in a 24 hour period (q.d. or once-daily), two times in a 24 hour period (b.i.d. or twice-daily) or three times in a 24 hour period (t.i.d. or three times daily) is provided.

Also provided, is a method of making a pharmaceutical or gastric retentive dosage form comprising a first dose of an opioid, a first dose of acetaminophen dispersed in an ER polymer matrix comprised of a polymer that swells upon imbibition of fluid to a size sufficient for gastric retention in the upper gastrointestinal tract in a fed mode.

In one embodiment, the method comprises wet granulation of a first mixture that comprises an opioid, acetaminophen and a binder to produce a first granulation mixture. In another embodiment, the wet granulating comprises spraying a solution of the binder and the opioid dissolved in water onto acetaminophen particles. In a further embodiment, the particles of the first granulation mixture are blended with a polymer and one or more excipients to form an ER portion of a dosage form.

In one embodiment, the one or more excipients blended with the first granulation mixture are chosen from among a filler, a lubricant and a color agent.

In one embodiment, the wet granulation comprises making a solution containing an opioid and a binder and spraying the solution onto the acetaminophen particles in a fluid bed granulator.

In a further embodiment, the method comprises compressing the ER portion of the dosage form into a tablet.

In one embodiment, the wet granulation of the ER portion of the dosage form produces particles with a bulk density ranging from about 0.30 to 0.40 grams/milliliter (g/ml). In other aspects, the wet granulation produces particles with a tap density ranging from about 0.35 g/ml to about 0.45 g/ml. In other embodiments, the wet granulation produces particles, wherein at least about 50% of the particles have a size greater than 250 μ . In still other embodiments, the wet granulation produces particles wherein about 20% to about 30% of the particles have a size greater than about 150 μ and less than about 250 μ .

In one embodiment, the method of making a pharmaceutical and/or gastric retentive oral dosage form comprising acetaminophen and an opioid further comprises wet granulating a second mixture comprising the acetaminophen, the opioid, and the binder to form a second granulation mixture. In a further embodiment, the second granulation mixture is blended with one or more excipients to produce an IR portion of the dosage form. In yet a further embodiment, the IR portion is compressed with the ER portion of the dosage form to produce a bilayer tablet.

In further embodiments, wet granulating the second mixture is achieved by fluid bed granulation. In other embodiments, wet granulating the second mixture is achieved by a high shear granulation method.

In an alternative embodiment, the method of making a pharmaceutical and/or gastric retentive oral dosage form comprising acetaminophen and an opioid comprises using a

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high-shear fluid bed granulator to prepare a first granulation mixture which comprises an opioid, a filler, and a first binder. In one embodiment, the first granulation mixture further comprises an antioxidant. In yet another embodiment, the first granulation mixture further comprises a metal ion chelator. In another embodiment, the method further comprises drying the first granulation mixture. In yet another embodiment, the method further comprises using a fluid-bed granulator to prepare a second granulation mixture comprising the first granulation mixture and acetaminophen. In yet another embodiment, the method further comprises blending the second granulation mixture with a hydrophilic polymer and one or more excipients to form an extended release portion. In yet another embodiment, the method further comprises compressing the extended release portion of the dosage form to form a monolithic tablet.

In one embodiment, the method of making a pharmaceutical and/or gastric retentive oral dosage comprises using a fluid-bed granulator to prepare a third granulation mixture which comprises the first granulation mixture, acetaminophen and a binder. In another embodiment, the method further comprises blending the third granulation mixture with a lubricant to form an immediate release portion. In yet another embodiment, the method further comprises compressing the extended release portion and the immediate release portion to form a bilayer tablet.

Also provided is a method of treating pain in a subject in need of such treatment comprising administering a therapeutic effective amount of any of the describe dosage forms or pharmaceutical formulations herein.

In one embodiment, a gastric retained dosage form comprising acetaminophen, an opioid and a swellable polymer is administered to a subject suffering from or diagnosed with a pain state. In other embodiments, the subject is suffering from chronic pain. In yet another embodiment, the subject is suffering from acute pain. In yet other embodiments, the subject is suffering from both chronic and acute pain.

In one embodiment, a gastric retained dosage form is administered to a subject in a fed mode. In another embodiment, the dosage form is administered with a meal to a subject once in a 24 hour period. In other embodiments, the dosage form is administered with a meal to the subject twice in a 24 hour period. In some embodiments, the dosage form is administered with a meal to the subject three times in a 24 hour period.

Additional embodiments of the present method, compositions, and the like will be apparent from the following description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment or aspect. Additional aspects and embodiments are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical representation of the dissolution profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO N-60K.

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FIG. 2 is a graphical representation of the dissolution profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO 1105.

FIG. 3 is a graphical representation of the dissolution release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 wt % POLYOX® PEO N-60K and 16.60 wt % MCC.

FIG. 4 is a graphical representation of the dissolution release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 (wt %) POLYOX® PEO 1105 and 16.60 wt % MCC.

FIG. 5 is a graphical representation of the dissolution profile of a 1000 mg tablet containing 31 weight percent POLYOX® PEO N-60K and varying amounts of microcrystalline cellulose.

FIG. 6 is a graphical representation of the disintegration profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO N-60K.

FIG. 7 is a graphical representation of the disintegration profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 vvt % POLYOX® PEO 1105.

FIG. 8 is a graphical representation of the disintegration release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 wt % POLYOX® PEO N-60K and 16.60 wt % MCC.

FIG. 9 is a graphical representation of the disintegration release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 wt % POLYOX® PEO 1105 and 16.60 wt % MCC.

FIG. 10 is a graphical representation of Phenylephrine (PE) release vs. the square root of time of a tablet having 24.28 wt % POLYOX® PEO N-60K (sample 1), and a tablet having 24.28 wt % POLYOX® PEO 1105 (sample 2).

FIG. 11 is a graphical representation of PE release vs. the square root of time generated by a tablet having 24.22 wt % POLYOX® PEO N-60K and 16.60 wt % MCC (sample 3) and a tablet having 24.22 wt % POLYOX® PEO 1105 and 16.60 wt % MCC (sample 4).

FIG. 12 is a graphical representation of the cumulative oxycodone disintegration release of tablets containing varying amounts of POLYOX® PEO N-60K or POLYOX® PEO 1105.

FIG. 13 is a graphical representation of the cumulative acetaminophen disintegration release of tablets containing varying amounts of POLYOX® PEO N-60K or POLYOX® PEO 1105.

FIG. 14 is a graphical representation of linear regression analysis of oxycodone and acetaminophen release for a dosage form described herein (lot number: 081104-03).

FIG. 15 is a graphical representation of linear regression analysis of oxycodone and acetaminophen release data for a dosage form as described herein (lot number: 081104-06).

FIG. 16 is a graphical representation of the cumulative acetaminophen and oxycodone HCl disintegration release of a bilayer tablet.

FIG. 17 is a graphical representation of the cumulative acetaminophen and oxycodone HCl disintegration release of a bilayer tablet.

FIG. 18 is a graphical representation of the particle size distribution as determined for an extended release polymer matrix.

FIG. 19 is a graphical representation of the particle size distribution as determined for an IR portion of a dosage form.

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FIG. 20 is a graphical representation of the cumulative acetaminophen and tramadol disintegration release of a bilayer tablet.

FIG. 21 is a graphical representation of the acetaminophen dissolution release profile for a bilayer tablet in which the IR layer contains hydroxypropylcellulose as a binder.

FIG. 22 is a graphical representation of the oxycodone hydrochloride dissolution release profile for a bilayer tablet in which the IR layer contains hydroxypropylcellulose as a binder.

FIG. 23 is a graphical representation of the cumulative acetaminophen and oxycodone HCl disintegration release of a bilayer tablet formulated for 8-hour release.

FIG. 24 is a graphical representation of the cumulative acetaminophen and oxycodone HCl disintegration release of a bilayer tablet formulated for 6-hour release.

FIG. 25 is a graphical representation of the cumulative acetaminophen and oxycodone HCl disintegration release of a bilayer tablet formulated for 8-hour release.

FIG. 26 is a graphical representation of the cumulative acetaminophen and oxycodone HCl disintegration release of a bilayer tablet formulated for 6-hour release.

FIG. 27 is a graphical representation of erosion of bilayer tablets containing acetaminophen and oxycodone HCl in vitro, in vivo and

DETAILED DESCRIPTION

The various aspects and embodiments will now be fully described herein. These aspects and embodiments may, however, be embodied in many different forms and should not be construed as limiting; rather, these embodiments are provided so the disclosure will be thorough and complete, and will fully convey the scope of the present subject matter to those skilled in the art.

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

I. Definitions

It must be noted that, as used in this specification, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

The term "about," particularly in reference to a given quantity, is meant to encompass deviations of plus or minus five percent.

Compounds useful in the compositions and methods include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, as well as racemic mixtures and pure isomers of the compounds described herein, where applicable.

"Pharmaceutically acceptable salt" includes, but is not limited to, amino acid salts, salts prepared with inorganic acids, such as chloride, sulfate, phosphate, diphosphate, bromide, and nitrate salts, or salts prepared from the corresponding inorganic acid form of any of the preceding, e.g., hydrochloride, etc., or salts prepared with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, ethylsuccinate, citrate, acetate, lactate, methanesulfonate, benzoate, ascorbate, para-toluenesulfonate, palmoate, salicylate and stearate, as well as estolate, gluceptate and lactobionate salts. Similarly salts containing pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium (including substituted ammonium).

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“Optional” or “optionally” means that the subsequently described element, component or circumstance may or may not occur, so that the description includes instances where the element, component, or circumstance occurs and instances where it does not.

The terms “subject,” “individual” or “patient” are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, humans.

The term “drug” or “active agent” is used herein to refer to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor from eliciting a physiological response.

The term “sparingly soluble,” as used herein, refers to a drug having a solubility (measured in water at 37° C.) in the range of about 0.001% to about 2% by weight, more preferably about 0.001% to about 0.5% by weight. The term “soluble,” as used herein, refers to a drug having a solubility (measured in water at 37° C.) in the range of about 2% to about 10% by weight, more preferably about 2% to about 5% by weight.

The term “fed mode,” as used herein, refers to a state which is typically induced in a patient by the presence of food in the stomach, the food giving rise to two signals, one that is said to stem from stomach distension and the other a chemical signal based on food in the stomach. It has been determined that once the fed mode has been induced, larger particles are retained in the stomach for a longer period of time than smaller particles. Thus, the fed mode is typically induced in a patient by the presence of food in the stomach.

Administration of a dosage form “with a meal,” as used herein, refers to administration before, during or after a meal, and more particularly refers to administration of a dosage form about 1, 2, 3, 4, 5, 10, 15 minutes before commencement of a meal, during the meal, or about 1, 2, 3, 4, 5, 10, 15 minutes after completion of a meal.

A drug “release rate,” as used herein, refers to the quantity of drug released from a dosage form or pharmaceutical composition per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically measured as an in vitro rate of dissolution, i.e., a quantity of drug released from the dosage form or pharmaceutical composition per unit time measured under appropriate conditions and in a suitable fluid. The specific results of dissolution tests claimed herein are performed on dosage forms or pharmaceutical compositions in a USP Type II apparatus and immersed in 900 ml of simulated intestinal fluid (SIF) at pH 6.8 and equilibrated in a constant temperature water bath at 37° C. Suitable aliquots of the release rate solutions are tested to determine the amount of drug released from the dosage form or pharmaceutical composition. For example, the drug can be assayed or injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

The term “swellable polymer,” as used herein, refers to a polymer that will swell in the presence of a fluid. It is understood that a given polymer may or may not swell when present in a defined drug formulation. Accordingly, the term “swellable polymer” defines a structural feature of a polymer which is dependent upon the composition in which the polymer is formulated. Whether or not a polymer swells in the presence of fluid will depend upon a variety of factors, including the specific type of polymer and the percentage of that polymer in a particular formulation. For example, the term “polyethylene oxide,” or “PEO” refers to a polyethylene

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oxide polymer that has a wide range of molecular weights. PEO is a linear polymer of unsubstituted ethylene oxide and has a wide range of viscosity-average molecular weights. Examples of commercially available PEOs and their approximate molecular weights are: POLYOX® NF, grade WSR coagulant, molecular weight 5 million, POLYOX® grade WSR 301, molecular weight 4 million, POLYOX® grade WSR 303, molecular weight 7 million, and POLYOX® grade WSR N-60K, molecular weight 2 million. It will be understood by a person with ordinary skill in the art that an oral dosage form which comprises a swellable polymer will swell upon imbibition of water or fluid from gastric fluid.

The term “friability,” as used herein, refers to the ease with which a tablet will break or fracture. The test for friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of formulation abraded or chipped is calculated. The friability of the tablets, of the present invention, is preferably in the range of about 0% to 3%, and values about 1%, or less, are considered acceptable for most drug and food tablet contexts. Friability which approaches 0% is particularly preferred.

The term “tap density” or “tapped density,” as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

The term “bulk density,” as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

The term “capping,” as used herein, refers to the partial or complete separation of top or bottom crowns of the tablet main body. For multilayer tablets, capping refers to separation of a portion of an individual layer within the multilayer tablet. Unintended separation of layers within a multilayer tablet prior to administration is referred to herein as “splitting.”

The term “content uniformity,” as used herein refers to the testing of compressed tablets to provide an assessment of how uniformly the micronized or submicron active ingredient is dispersed in the powder mixture. Content uniformity is measured by use of USP Method (General Chapters, Uniformity of Dosage Forms), unless otherwise indicated. A plurality refers to five, ten or more tablet compositions.

II. Gastric Retentive Extended Release Dosage Form

It has been surprisingly discovered that a pharmaceutically acceptable gastric retentive dosage form can be formulated to provide release in the stomach of a combination of a sparingly soluble drug and a highly soluble drug at rates proportional to one another over an extended period of time. Described herein is a pharmaceutically acceptable dosage form for the treatment of pain in a subject, comprising an opioid and acetaminophen dispersed in a polymer matrix that, upon oral administration, swells dimensionally unrestrained, with the imbibition of fluid to a size sufficient for gastric retention in a stomach of a subject in a fed mode. In the presently described

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dosage form, acetaminophen is released from the dosage form through erosion and an opioid also present in the dosage form is released at a rate proportional to that of the acetaminophen. This proportional rate of release may occur over a period of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours or more.

Gastric retentive dosage forms described herein typically contain at least one hydrophilic polymer in a water-swellaible polymer matrix having at least one drug dispersed therein. The polymer matrix, wherein the at least one drug is dispersed, absorbs water, causing the matrix to swell, which in turn promotes retention of the dosage form in the upper gastrointestinal tract (GI) of a subject. In addition, the matrices become slippery, which provides resistance to peristalsis and further promotes gastric retention.

The imbibition of water and subsequent swelling also allows drugs to diffuse out of the matrix, to be released from the matrix as a result of physical erosion, i.e., degradation, or a combination of the two. Whether the drugs are released via diffusion or erosion depends, in part, on the solubility of the drug in the relevant environment.

Thus, successful formulation of effective oral pharmaceutical dosage forms may be highly dependent upon the solubility of the incorporated drugs. For example, compositions in a tablet may differ when the tablet contains a high solubility drug as compared to when the tablet contains a low solubility drug.

With the dosage forms described herein, the rate at which the drugs are released by the gastric retentive dosage form into the gastrointestinal tract is largely dependent on the rate at and the degree to which the polymer matrix swells and. The polymer used in the dosage forms of the present invention should not release the drug at too rapid a rate so as to result in a drug overdose or rapid passage into and through the gastrointestinal tract, nor should the polymer release drug too slowly to achieve the desired biological effect. Thus, polymers that permit a rate of drug release that achieves the requisite pharmacokinetics for both the acetaminophen and the opioid for a desired duration, as may be determined using a USP Disintegration Test or Dissolution Test, are determined for use in the dosage forms described herein.

Polymers suitable for use in the dosage forms described herein include those that both swell upon absorption of gastric fluid and gradually erode over a time period of hours. Upon swelling of the polymer matrix, soluble drugs dispersed in the matrix will slowly dissolve in the permeating fluid and diffuse out from the matrix. Drugs that are poorly, or sparingly, soluble are released primarily via erosion of the polymer matrix. Erosion initiates simultaneously with the swelling process, upon contact of the surface of the dosage form with gastric fluid. Erosion reflects the dissolution of the polymer beyond the polymer gel-solution interface where the polymer has become sufficiently dilute that it can be transported away from the dosage form by diffusion or convection. This may also depend on the hydrodynamic and mechanical forces present in the gastrointestinal tract during the digestive process. While swelling and erosion occur at the same time, it is preferred herein that drug release should be erosion-controlled, meaning that the selected polymer should be such that complete drug release occurs primarily as a result of erosion rather than swelling and dissolution. However, swelling should take place at a rate that is sufficiently fast to allow the tablet to be retained in the stomach. At minimum, for an erosional gastric retentive dosage form, there should be an extended period during which the dosage form maintains its size before it is diminished by erosion. Furthermore, the polymer which imbibes fluid to form a gastric retained, extended release polymer matrix is any polymer that is non-

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toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of at least one incorporated drug.

Suitable polymers for use in the present dosage forms may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, if copolymers, either random copolymers, block copolymers or graft copolymers. Synthetic hydrophilic polymers useful herein include, but are not limited to: polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers; cellulosic polymers; acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate; maleic anhydride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate.

Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone), starch and starch-based polymers, poly(2-ethyl-2-oxazoline), poly(ethyleneimine), polyurethane hydrogels, and crosslinked polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers.

The terms "cellulose" and "cellulosic" are used herein to denote a linear polymer of anhydroglucose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C.

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The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 50% of the drugs within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 55%, 60%, 65%, 70%, 75%, or 80% of the drugs remains in the extended release matrix one hour after ingestion. The amount of polymer is such that at least 20%, 25%, 30%, 35%, 40% or 45% of the drugs remains in the extended release matrix four hours after ingestion. The amount of polymer is such that at least 75%, 80%, or 85% of the drugs is released within six hours after ingestion. In all cases, however, the drugs will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

The water-swellaible polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

As discussed above, the gastric retentive nature and release profiles of a dosage form will depend partially upon the molecular weight of the swellaible polymer. The polymers are preferably of a moderate to high molecular weight (900,000 Da to 4,000,000 Da) to enhance swelling and provide control of the release of the opioid and acetaminophen via erosion of the polymer matrix. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of 900,000 Da to 2,000,000 Da. Using a lower molecular weight ("MW") polyethylene oxide, such as POLYOX™ 1105 (900,000 MW) release for both drugs are higher. Using a higher molecular weight polyethylene oxide (such as POLYOX™ N-60K (2,000,000 MW) or POLYOX™ WSR-301 (4,000,000 MW) reduces the rate of release for both drugs. In one embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight is utilized so that the viscosity of a 1% aqueous solution is about 4000 cps to greater than 100,000 cps.

A typical dosage form should swell to approximately 115% of its original volume within 30 minutes after administration, and at a later time should swell to a volume that is 130% or more of the original volume.

The acetaminophen and opioid are dispersed within the polymeric matrix described above. The acetaminophen as used herein is preferably a USP powder. Such powders of acetaminophen are known in the art as difficult to compress into tablet forms. In alternative gastric retentive extended release oral dosage forms comprising acetaminophen and an opioid, the acetaminophen used may be a milled form, for example, various COMPAP® compositions (Mallinckrodt, Inc.). In certain embodiments, the opioid analgesic is selected from tramadol, oxycodone, hydrocodone, hydromorphone, oxymorphone, methadone, morphine, or codeine, or pharmaceutically acceptable salts thereof.

Dosage forms prepared for oral administration according to the present disclosure will generally contain other inactive additives (excipients) such as binders, lubricants, disinte-

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grants, fillers, stabilizers, antioxidants, chelating agents, surfactants, coloring agents, and the like. The excipients described below may be present in the ER layer, the IR layer or both layers.

Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, microcrystalline cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum.

Lubricants are used to facilitate tablet manufacture, promoting powder flow and preventing particle capping (i.e., particle breakage) when pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25 wt % to 3 wt %, preferably 0.2 wt % to 1.0 wt %, more preferably about 0.3 wt %), calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids at about 1 wt % to 5 wt %, most preferably less than about 2 wt %).

Disintegrants are used to facilitate disintegration of the tablet, thereby increasing the erosion rate relative to the dissolution rate, and are generally starches, clays, celluloses, algin, gums, or crosslinked polymers (e.g., crosslinked polyvinyl pyrrolidone). Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, lactose monohydrate, dextrose, sodium chloride, and sorbitol. Solubility-enhancers, including solubilizers per se, emulsifiers, and complexing agents (e.g., cyclodextrins), may also be advantageously included in the present formulations.

Stabilizers, as well known in the art, are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions.

Chelating agents tend to form complexes with trace amount of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments. Chelating agents for use in the dosage forms described herein include, but are not limited to, ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo) tetraacetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N'',N'''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazocyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N''-tetraacetic acid.

Anti-oxidant may increase the stability of the dosage form by increasing the stability of the active ingredient as well as the dosage form as a whole. The anti-oxidant may be selected from ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, or propylgallate, or any combination of the above.

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The formulations are typically in the form of tablets. Other formulations contain the matrix/active agent particles in capsules. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts, e.g., in Gennaro, A. R., editor. "Remington: The Science & Practice of Pharmacy", 21st ed., Williams & Williams, and in the "Physician's Desk Reference", 2006, Thomson Healthcare.

The tablets described herein may have individual layers containing one or both drugs for delivering the component drug(s) in the immediate release or the extended release mode. For example, a layer for immediate release of acetaminophen or both acetaminophen and opioid can be added to the layer containing both drugs for extended release. As to acetaminophen in this embodiment, although at steady state, unlike single dose administration, bioavailability is quite constant between the doses of 325 mg and 2000 mg. This may be desirable for prompt relief or bioavailability enhancement due to first-pass metabolism of acetaminophen or the particular opioid.

Alternative gastric retentive drug delivery systems include the swellable bilayer described by Franz, et al., U.S. Pat. No. 5,232,704; the multi-layer tablet with a band described by Wong, et al., U.S. Pat. No. 6,120,803; the membrane sac and gas generating agent described in Sinnreich, U.S. Pat. No. 4,996,058; the swellable, hydrophilic polymer system described in Shell, et al., U.S. Pat. No. 5,972,389, and Shell, et al., WO 9855107, and the pulsatile gastric retentive dosage form by Cowles et al., U.S. Pub. No. 2009/0028941, all of which are incorporated herein by reference.

A bilayer tablet can be made with one layer containing only the opioid and the second layer containing only the acetaminophen if a substantially different release profile for each drug is desired if the two drugs are not chemically compatible.

It is also envisioned that a third layer containing one or more drugs for immediate release can be added to the dosage form.

Thus, the dosage forms provide controlled delivery of acetaminophen, and an opioid analgesic to the upper GI tract by a polymer matrix that swells unrestrained dimensionally, and is retained in the stomach when taken with food, i.e., in the fed mode. In an environment of use, the dosage forms swell on contact with water from gastric fluid due to the component hydrophilic polymers, (for example, polyethylene oxide and/or hypromellose), and increase in size to be retained in the fed stomach. Acetaminophen and an opioid, for example oxycodone, hydrocodone, or codeine, will be released from these gastric retained dosage forms over an extended period of time, about 3 to about 12 hours, preferably about 4 to about 9 hours, more preferably at least about 5 hours, to the upper gastrointestinal (GI) tract where acetaminophen, and potentially the opioid, is best absorbed,

It is also notable that the presence of an opioid in a gastric retentive dosage form may adversely affect the ability of a dosage form to erode at a rate that allows the desired release rates for the active agents. This is due to the fact that administration of opioids is known to reduce gastric motility (Nimmo et al., Br. J. Clin. Pharmac. (1975) 2:509-513). The reduced gastric motility, in turn, may reduce the ability of the dosage form to erode and release the drug within the erodible matrix.

Studies presented herein show that co-administration to dogs of a gastric retentive dosage form and a solution of

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opioid in amounts to simulate release by the embodied immediate release component have no significant effects on erosion of the gastric retentive extended release dosage forms. Furthermore, studies are done with the disclosed gastric retentive tablet which comprises both the extended release and immediate release drug layers to show the presence of opioid in the described dosage forms does not significantly affect erosion of the tablets in the dog stomach.

The pharmaceutically acceptable dosage form described herein further comprises an immediate release component. The immediate release component comprises acetaminophen and an opioid at lower amounts as compared to the amounts of the opioid and the acetaminophen the gastric retained extended release portion of the dosage form. In another aspect, the amount of acetaminophen in generally between about 10 to 20, more typically between 12 to 16 times the amount of opioid in the immediate release component.

In a preferred aspect, the immediate release component is in contact with the extended release component.

The immediate release component may further comprise excipients such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like, as described above for the extended release component.

The immediate release component may release at least 80-100% of the active agents within the first hour of oral administration.

Is it understood by the skilled artisan that delivery time or duration of drug release by a particular dosage form is distinct from the duration of drug delivery by the dosage form. As an example, while an extended release dosage form may release one or more drugs over a period of 3, 4 or more hours, depending on the half-life of the drug and the time of transit of that drug through the gastrointestinal tract, the relevant sites of absorption will be exposed for a period of time beyond the time of drug release from the dosage form. Thus, for example, a dosage form that releases one or more drugs over a period of approximately 8 hours may be providing delivery of that drug for a period of approximately 12 hours.

The dosage form, as presently described, possesses the additional advantageous feature of being formulated as a standard oral dosage size, then after administration, imbibing water from the gastric fluid and swelling to a size large enough to be retained in the stomach in a fed mode.

III. Methods for Making Solid Dosage Forms

The presently described dosage forms provide for extended release of both acetaminophen and an opioid in the stomach at rates proportional to one another wherein the dosage forms are comprised of a polymer matrix that swells upon imbibition of fluid to a size sufficient for gastric retention. Thus, in formulating the dosage forms, it is critical to provide the properties which simultaneously allow: a) an extent of swelling to provide gastric retention over an extended period, and b) a rate of swelling and erosion that allows extended and proportional release of both a highly soluble and poorly soluble drug.

Furthermore, the formulation of these pharmaceutical oral dosage forms preferably result in final products that meet the requirements of the Food and Drug Administration (FDA). For example, final products preferably have a stable product that does not fracture during storage and transport. This is measured, in part, in terms of friability and hardness. Dosage forms preferably also meet the requirements for content uniformity, which essentially means that the dispersion of the active ingredient(s) is uniform throughout the mixture used to make the dosage form, such that the composition of tablets

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formed from a particular formulation does not vary significantly from one tablet to another. The FDA requires a content uniformity within a range of 95% to 105%. Moreover, the active ingredients within the dosage forms should remain stable for long periods of time as required for standard consumer use. For example, it is very helpful to provide formulations that protect the active ingredients from undergoing, for example, oxidative degradation.

It is significant to note that acetaminophen can be a particularly challenging pharmaceutical ingredient with which to formulate solid oral dosage forms. Acetaminophen powders are difficult to compress into a tablet form which will not break or fall apart.

The ability to formulate a pharmaceutical oral dosage form which both delivers the desired therapeutically effective ingredient and meets FDA requirements depends, in part, upon the process by which the product is made.

In the case of tablets, as disclosed herein, a first step may involve the granulation. How the granulation is carried out has great impact on the properties of the final product.

Granulation is a manufacturing process which increases the size and homogeneity of active pharmaceutical ingredients and excipients which comprise a solid dose formulation. The granulation process, which is often referred to as agglomeration, changes important physical characteristics of the dry formulation, with the aim of improving manufacturability and, thereby, product quality, as well as providing desired release kinetics. As an example, water-soluble active agents may be granulated with dissolution-retarding materials such as polymers to provide an additional barrier. Such a process may reduce the release-rate of a water-soluble active agent. In the present embodiments, wherein the dosage form comprises a poorly soluble active agent (e.g., acetaminophen) with a highly soluble opioid (e.g., oxycodone HCl), the opioid may be granulated separately from the poorly soluble agent in order to retard the dissolution of the opioid. Moreover, depending upon the polymers applied to the water-soluble active agent, the extent of the diffusion rate of the active agents within a polymer (e.g., PolyOx) matrix may be manipulated to produce the desired release profiles, i.e., one may individually control the release rates of multiple active agents within a dosage form, wherein the active agents have different solubilities. Dissolution-retarding components include, but are not limited to, water soluble or non-water soluble polymers, hydrogel polymers, pH sensitive polymers or any combination thereof in a desired ratio.

Granulation technology can be classified into one of two basic types: Wet granulation and dry granulation. Wet granulation is by far the more prevalent agglomeration process utilized within the pharmaceutical industry.

Most wet granulation procedures follow some basic steps; the drug(s) and excipients are mixed together, and a binder solution is prepared and added to the powder mixture to form a wet mass. The moist particles are then dried and sized by milling or by screening through a sieve. In some cases, the wet granulation is "wet milled" or sized through screens before the drying step. There are four basic types of wet granulation; high shear granulation, fluid bed granulation, extrusion and spheronization and spray drying.

A. Fluid Bed Granulation

The fluid bed granulation process involves the suspension of particulates within an air stream while a granulation solution is sprayed down onto the fluidized bed. During the process, the particles are gradually wetted as they pass through the spray zone, where they become tacky as a result of the moisture and the presence of binder within the spray solution.

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These wetted particles come into contact with, and adhere to, other wetted particles resulting in the formation of particles.

A fluid bed granulator consists of a product container into which the dry powders are charged, an expansion chamber which sits directly on top of the product container, a spray gun assembly, which protrudes through the expansion chamber and is directed down onto the product bed, and air handling equipment positioned upstream and downstream from the processing chamber.

The fluidized bed is maintained by a downstream blower which creates negative pressure within the product container/expansion chamber by pulling air through the system. Upstream, the air is "pre-conditioned" to target values for humidity, temperature and dew point, while special product retention screens and filters keep the powder within the fluid bed system.

As the air is drawn through the product retention screen it "lifts" the powder out of the product container and into the expansion chamber. Since the diameter of the expansion chamber is greater than that of the product container, the air velocity becomes lower within the expansion chamber. This design allows for a higher velocity of air to fluidize the powder bed causing the material to enter the spray zone where granulation occurs before losing velocity and falling back down into the product container. This cycle continues throughout the granulation process.

The fluid bed granulation process can be characterized as having three distinct phases; pre-conditioning, granulation and drying. In the initial phase, the process air is pre-conditioned to achieve target values for temperature and humidity, while by-passing the product container altogether. Once the optimal conditions are met, the process air is re-directed to flow through the product container, and the process air volume is adjusted to a level which will maintain sufficient fluidization of the powder bed. This pre-conditioning phase completes when the product bed temperature is within the target range specified for the process.

In the next phase of the process, the spraying of the granulating solution begins. The spray rate is set to a fall within a pre-determined range, and the process continues until all of the solution has been sprayed into the batch. It is in this phase where the actual granulation, or agglomeration, takes place.

Once the binder solution is exhausted, the product continues to be fluidized with warm process air until the desired end-point for moisture content is reached. This end-point often correlates well with product bed temperature, therefore in a manufacturing environment, the process can usually be terminated once the target product bed temperature is reached. A typical fluid bed process may require only about thirty to forty-five minutes for the granulation step, plus ten to fifteen minutes on either side for pre-conditioning and drying.

As with any of the wet granulation processes, the most important variable is the amount of moisture required to achieve successful agglomeration. The fluid bed granulation process requires a "thermodynamic" balance between process air temperature, process air humidity, process air volume and granulation spray rate. While higher process air temperature and process air volume add more heat to the system and remove moisture, more granulating solution and a higher solution spray rate add moisture and remove heat via evaporative cooling. These are the critical process parameters which preferably are evaluated as a manufacturing process is developed, and the key is understanding the interdependency of each variable.

Additional factors affecting the outcome of the fluid bed granulation process are the amount and type of binder solution, and the method by which the binder is incorporated

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within the granulation. However, the most important process variables are the total amount of moisture added through the process, and the rate at which the moisture content is increased. These parameters can have a significant effect on the quality and the characteristics of the granulation. For instance, a wetter fluid bed granulation process tends to result in a stronger granule with a higher bulk density. However, an overly aggressive process, where moisture is added too rapidly, can lose control over achieving the final particle size and particle size distribution objectives.

"Fluid-bed granulating," as used herein, refers to the method of preparing granules using a fluid bed granulation process as understood by one having ordinary skill in the art.

B. High Shear Granulation

Most pharmaceutical products manufactured by wet granulation utilize a high shear process, where blending and wet massing are accomplished by the mechanical energy generated by an impeller and a chopper. Mixing, densification and agglomeration are achieved through the "shear" forces exerted by the impeller; hence the process is referred to as high shear granulation.

"High shear granulating," as used herein, refers to the method of preparing granules using a high shear granulation process as understood by one having ordinary skill in the art.

The process begins by adding the dry powders of the formulation to the high shear granulator, which is a sealed "mixing bowl" with an impeller which rotates through the powder bed, and a chopper blade which breaks up over-agglomerates which can form during the process. There are typically three phases to the high shear process; dry mixing, solution addition, or wet massing and high shear granulation.

In the first phase, dry powders are mixed together by the impeller blade which rotates through the powder bed. The impeller blade is positioned just off the bottom of the product container. There is a similar tolerance between the tips of the impeller blade and the sides of the container. The impeller blades rotation through the powder bed creates a "roping" vortex of powder movement. The dry mixing phase typically lasts for only a few minutes.

In the second phase of the process, a granulating liquid is added to the sealed product container, usually by use of a peristaltic pump. The solution most often contains a binder with sufficient viscosity to cause the wet massed particles to stick together or agglomerate. It is common for the solution addition phase to last over a period of from three to five minutes. While the impeller is rotating rather slowly during this step of the process, the chopper blade is turning at a fairly high rate of speed, and is positioned within the product container to chop up over-sized agglomerates, while not interfering with the impellers movement.

Once the binder solution has been added to the product container, the final stage of the granulation process begins. In this phase, high shear forces are generated as the impeller blades push through the wet massed powder bed, further distributing the binder and intimately mixing the ingredients contained therein. The impeller and chopper tool continue to rotate until the process is discontinued when the desired granule particle size and density end-points are reached. This end-point is often determined by the power consumption and/or torque on the impeller.

Once the high shear granulation process has been completed, the material is transferred to a fluid bed dryer, or alternatively, spread out onto trays which are then placed in a drying oven, where the product is dried until the desired moisture content is achieved, usually on the order of 1-2% as measured by Loss On Drying technique.

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The most important variable which affects the high shear process is the amount of moisture required to achieve a successful granulation. A key to the process is having the right amount of moisture to allow for agglomeration to occur. Too little moisture will result in an under-granulated batch, with weak bonds between particles and smaller, to non-existent particles, with properties similar to those of the dry powder starting materials. On the other hand, excess moisture can result in a "crashed" batch with results varying from severe over-agglomeration to a batch which appears more like soup.

Other critical formulation parameters affecting the outcome of the high shear granulation process are the amount and type of binder solution, and the method by which the binder is incorporated within the granulation. For example, it is possible to include some of the binder in the dry powder mixture as well as in the granulating solution, or it may be incorporated only in the granulating solution or only in the dry powder, as is the case where water is used as the granulating solution.

The high shear granulation process parameters which are variable include impeller and chopper speeds, the solution addition rate, and the amount of time allocated to the various phases of the process. Of these, the most important variables are the solution addition rate and the amount of time the wet massed product is under high shear mixing.

C. Extrusion and Spheronization

This specialized wet granulation technique involves multiple processing steps and was developed to produce very uniform, spherical particles ideally suited for multi-particulate drug delivery of delayed and sustained release dosage forms.

Similar to high shear granulation initially, the first step involves the mixing and wet massing of the formulation. Once this step is complete, the wet particles are transferred to an extruder which generates very high forces used to press the material out through small holes in the extruder head. The extrudate is of uniform diameter and is then transferred onto a rotating plate for spheronization. The forces generated by the rotating plate initially break up the extruded formulation strands into uniform lengths. Additional dwell time within the spheronizer creates particles which are quite round and very uniform in size. These pellets or spheres may then be dried to the target moisture content, usually within a fluid bed system.

Particles produced in this manner tend to be very dense, and have a capacity for high drug loading, approaching 90% or more in some cases. Importantly, the particle size is very uniform, and the size distribution is very narrow, as compared to other granulation approaches. This quality assures consistent surface area within and between batches, which is extremely important when functional coatings are subsequently applied to create sustained release formulations, delayed release formulations and formulations designed to target a specific area within the body.

Uniform surface area is important because the pharmaceutical coating process endpoint is determined not by coating thickness, but by the theoretical batch weight gain of the coating material. If the batch surface area is consistent, then the coating thickness will also be consistent for a given weight gain, and coating thickness is the primary variable in determining the functionality of the coating system, whether the goal is controlling the duration of sustained release formulations or imparting an acid resistant characteristic to "beads" necessary to protect certain compounds which would otherwise be severely degraded in the presence of the acidic environment of the stomach.

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D. Spray Drying

Spray drying is a unique and specialized process which converts liquids into dry powders. The process involves the spraying of very finely atomized droplets of solution into a "bed" or stream of hot process air or other suitable gas. Not typically utilized for the conventional granulation of dosage form intermediates, spray drying has gained acceptance within the industry as a robust process which can improve drug solubility and bioavailability.

Spray drying can be used to create co-precipitates of a drug/carrier which can have improved dissolution and solubility characteristics. In addition, the process can also be useful as a processing aid. For example, it is much more difficult to maintain the uniformity of a drug in suspension, as compared to the same compound in solution. One may have a need to develop an aqueous coating or drug layering process utilizing a drug which is otherwise not soluble in water. By creating a co-precipitate of the drug and a suitable water soluble carrier, often a low molecular weight polymer, the co-precipitate will remain in solution throughout the manufacturing process, improving uniformity of the spray solution and the dosage form created by the coating process. Uniformity is particularly important where lower doses of potent compounds are intended to be coated onto beads or tablet cores.

This same process may be used to enhance the solubility and bioavailability of poorly soluble drugs. By complexing certain excipients and the active ingredient within a solvent system which is then spray dried, it is possible to enhance the drugs absorption within the body. Selection of the solvent system, the complexing agent(s) and the ratios utilized within the formulation are all important formulation variables which determine the effectiveness of solubility enhancement utilizing the spray drying technique. Important process parameters which also have a profound effect on drug solubility are the temperatures of the spray solution and process gas, the spray rate and droplet size and the rate of re-crystallization. The spray dried granulations created by these techniques can then be incorporated into capsules or tablets by conventional manufacturing processes.

E. Dry Granulation

The dry granulation process involves three basic steps; the drug(s) and excipients(s) are mixed (along with a suitable binder if needed) and some form of lubrication, the powder mixture is compressed into dry "compacts," and then the compacts are sized by a milling step. The two methods by which dry granulation can be accomplished are slugging and roller compaction.

**IV. Methods of Making the Extended Release
Gastric Retentive Dosage Forms Disclosed Herein**

In one aspect, a method of making a gastric retentive extended-release dosage form as a single layer tablet comprising wet granulation of the opioid and the acetaminophen with the binder is provided. The wet granulation can be a fluid-bed or high shear granulation method. The granulated particles are then blended with additional excipients as needed to form a mixture which is then compressed to form tablets.

Extended release polymer matrices comprising acetaminophen and an opioid are made using either POLYOX™ 1105 (approximate molecular weight of 900,000 Daltons), POLYOX™ N-60K (approximate molecular weight of 2,000,000 Daltons), or POLYOX™ WSR-301 (approximate molecular weight of 4,000,000 Daltons). Prior to compression, components are granulated using a top spray fluid bed

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granulator A solution of povidone (PVP) in water is sprayed onto the acetaminophen and fluid-bed granulated.

After fluid bed granulation and drying of the resultant particles, batches are characterized with respect to properties such as final Loss on Drying (LOD), bulk density, tap density, and particle size.

Loss on Drying (LOD) is determined after each granulation using the Moisture Analyzer. A 1 g samples are taken and loaded into the moisture analyzer. The sample is run for 5 minutes at a temperature of 105° C.

Bulk and tap densities can be determined as follows. A graduated cylinder is filled with a certain amount of material (82-88 g), and the volume recorded to determine the material bulk density. Tap density can be determined with a help of a Tap Density Tester by exposing the material to 100 taps per test and recording the new volume.

Particle size determination is performed immediately after granulation, after sieving through 20 mesh screen to remove agglomerates. Particle diameter is determined with a sieve-type particle diameter distribution gauge using sieves with openings of 44, 53, 75, 106, 150, and 250 mesh. Fractions are weighed on Mettler balance to estimate size distribution. This provides determination of the quantitative ratio by particle diameter of composition comprising extended release particles. Sieve analysis according to standard United States Pharmacopoeia methods (e.g., USP-23 NF 18), may be done such as by using a Meinzer II Sieve Shaker.

The granulated mixture can be blended with the polymer, filler and lubricant in a V-blender. The resultant mixture can be compressed into monolithic, single-layer tablets using a Manesty® BB4 press, with a modified oval 0.3937" widthx 0.6299" lengthx0.075" cup depth tool. Tablets may be prepared at a rate, for example, of approximately 800 tablets per minute.

Tablets are then characterized with respect to disintegration and dissolution release profiles as well as tablet hardness, friability and content uniformity.

In vitro dissolution profiles for the tablets may be determined in USP apparatus (40 mesh baskets), 100 rpm, in pH 5.8 phosphate buffer (0.1N HCl), 37° C. Samples of 5 ml at each time-point, may be taken without media replacement at 1, 2, 4, 6, 8 and 12 hours. In some embodiments, the dissolution profiles may be determined at varying pH values, such as at a pH of about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 or 6.5. The fluid used may be, for example, HCl, phosphate buffer or simulated gastric fluid. The resulting cumulative dissolution profiles for the tablets are, based upon a theoretical percent active added to the formulations.

A tablet preferably disintegrates before it dissolves. A disintegration tester measures the time it takes a tablet to break apart in solution. The tester suspends tablets in a solution bath for visual monitoring of the disintegration rate. Both the time to disintegration and the disintegration consistency of all tablets are measured. The disintegration profile may be determined in a USP Disintegration Tester in pH 5.8 phosphate buffer. In some embodiments, the disintegration profiles may be determined at varying pH values, such as at a pH of about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0 or 6.5. The fluid used may be, for example, HCl, phosphate buffer, or simulated gastric fluid. Samples, 1 ml at each time-point, may be taken, for example, without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profiles are based upon a theoretical percent active added to the formulation is determined.

Tablet hardness changes rapidly after compression as the tablet cools. A tablet that is too hard may not break up and dissolve into solution before it passes through the body. In the

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case of the presently disclosed gastric retentive dosage forms, a tablet that is too hard may not be able to imbibe fluid rapidly enough to prevent passage through the pylorus in a stomach in a fed mode. A tablet that is too soft may break apart, not handle well, and can create other defects in manufacturing. A soft tablet may not package well or may not stay together in transit.

After tablets are formed by compression, it is desired that the tablets have a strength of at least 9-25 Kiloponds (Kp)/cm², preferably at least about 12-20 (Kp)/cm². A hardness tester is used to determine the load required to diametrically break the tablets (crushing strength) into two equal halves. The fracture force may be measured using a Venkel Tablet Hardness Tester, using standard USP protocols.

Friability is a well-known measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability properties are especially important during any transport of the dosage form as any fracturing of the final dosage form will result in a subject receiving less than the prescribed medication. Friability can be determined using a Roche Friability Drum according to standard USP guidelines which specifies the number of samples, the total number of drum revolutions and the drum rpm to be used. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability.

The prepared tablets are tested for content uniformity to determine if they meet the pharmaceutical requirement of <6% relative standard deviation (RSD). Each tablet is placed in a solution of 1.0 N HCl and stirred at room temperature until all fragments have visibly dissolved. The solution containing the dissolved tablet is analyzed by HPLC.

In another aspect, a method of making a bilayer tablet comprising a gastric retentive extended-release layer and an immediate release layer is provided. In a further aspect, the gastric retentive extended-release layer is wet-granulated using the fluid bed or high shear granulation process. In yet a further aspect, the immediate release layer is wet-granulated using the fluid bed or high shear granulation process.

In another aspect, a dosage form for release of acetaminophen and an opioid is provided. The dosage form has an immediate release component and an extended release component, each of the components comprising acetaminophen and an opioid. The dosage form when placed in a USP Disintegration test with 800 mL aqueous buffer at pH 1.2 (0.1N HCl) at 37° C. apparatus provides an in vitro release of acetaminophen rate wherein 40-65% acetaminophen is released after 1 hour, 55-80% acetaminophen is released after 2 hours and at least about 75% acetaminophen is released after 6 hours. In one embodiment, the amount of opioid released is within about 20%, more preferably 15%, still more preferably within about 10% or 5% of the amount of acetaminophen released between 1-6 hours, more preferably 1-8 hours.

In another embodiment, the immediate release component of the dosage form releases at least about 70% of the dose of acetaminophen in the immediate release component after 1 hour in a USP disintegration tester with 800 mL aqueous buffer at pH 1.2 at 37° C. and at least about 70% of the dose of opioid in the same test. In another embodiment, the controlled release component of the dosage form releases at least about 40% of the dose of acetaminophen in the controlled release component after 6 hours and at least about 70% of the dose of acetaminophen in the controlled release component after 10 hours, when tested in a USP disintegration tester with 800 mL aqueous buffer at pH 1.2 at 37° C. The dose opioid released from the controlled release component is within

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about 20%, more preferably 15%, still more preferably within about 10% or 5% of the amount of acetaminophen released from the controlled release component over the desired period of sustained delivery, typically up to 6 hours, more preferably 8 hours.

In still another embodiment, the dosage form is a tablet comprised of an immediate release layer in direct contact with a sustained release, gastric retentive layer. The tablet when placed in a USP Disintegration test apparatus with 800 mL aqueous buffer at pH 1.2 (0.1N HCl) at 37° C. provides an in vitro release such that between 40-65% acetaminophen is released after 1 hour, more preferably between 45-60%, and the amount of opioid released is within about 15%, 10%, or 5% of the amount of acetaminophen released; and between 55-80% acetaminophen is released after 2 hours, more preferably between 60-75%, and the amount of opioid released is within about 15%, 10%, or 5% of the amount of acetaminophen released at this time point.

In still another embodiment, the dosage form is a tablet comprised of an immediate release layer in direct contact with a sustained release, gastric retentive layer. The tablet when placed in a USP Disintegration test apparatus with 800 mL aqueous buffer at pH 1.2 (0.1N HCl) at 37° C. provides an in vitro release such that between 10-25% acetaminophen is released after 1 hour, and the amount of opioid released is within about 15%, 10%, or 5% of the amount of acetaminophen released; and between 30-45% acetaminophen is released after 2 hours, and the amount of opioid released is within about 15%, 10%, or 5% of the amount of acetaminophen released at this time point.

In another embodiment, release of acetaminophen and opioid from the controlled release component of the dosage form is achieved by erosion of the controlled release component and diffusion of the drug. In one embodiment, release of acetaminophen from the controlled release component is achieved by erosion of one or more polymer components in the layer to expose the acetaminophen to the external environment for release of the drug. In another embodiment, release of the opioid from the controlled release component of the dosage form is achieved by erosion of the controlled release component and diffusion of the opioid through a hydrated polymer layer in the controlled release component. The cumulative percent of opioid released is linear when plotted as a function of square root of time for at least a period of 2 hours, more preferably 4 hours.

V. Methods of Treating Pain

In another aspect, a subject suffering from pain or at risk of experiencing pain is treated by oral administration of a gastric retentive extended release dosage form as described above. Treatment of both acute pain and chronic pain are contemplated.

The method of the present invention is useful for treating numerous pain states that are currently being treated with conventional immediate formulations comprising acetaminophen and/or opioid. These and additional pain states include, by way of illustration and not limitation, headache pain, pain associated with migraine, neuropathic pain selected from the group consisting of diabetic neuropathy, HIV sensory neuropathy, post-herpetic neuralgia, post-thoracotomy pain, trigeminal neuralgia, radiculopathy, neuropathic pain associated with chemotherapy, reflex sympathetic dystrophy, back pain, peripheral neuropathy, entrapment neuropathy, phantom limb pain, and complex regional pain syndrome, dental pain, pain associated with a surgical procedure and or other medical intervention, bone cancer pain, joint pain

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associated with psoriatic arthritis, osteoarthritic pain, rheumatoid arthritic pain, juvenile chronic arthritis associated pain, juvenile idiopathic arthritis associated pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome)) associated pain, pain associated with psoriatic arthritis, gout pain, pain associated with pseudogout (pyrophosphate arthritis), pain associated with systemic lupus erythematosus (SLE), pain associated with systemic sclerosis (scleroderma), pain associated with Behcet's disease, pain associated with relapsing polychondritis, pain associated with adult Still's disease, pain associated with transient regional osteoporosis, pain associated with neuropathic arthropathy, pain associated with sarcoidosis, arthritic pain, rheumatic pain, joint pain, osteoarthritic joint pain, rheumatoid arthritic joint pain, juvenile chronic arthritis associated joint pain, juvenile idiopathic arthritis associated joint pain, Spondyloarthropathies (such as ankylosing spondylitis (Mb Bechterew) and reactive arthritis (Reiter's syndrome)) associated joint pain, gout joint pain, joint pain associated with pseudogout (pyrophosphate arthritis), joint pain associated with systemic lupus erythematosus (SLE), joint pain associated with systemic sclerosis (scleroderma), joint pain associated with Behcet's disease, joint pain associated with relapsing polychondritis, joint pain associated with adult Still's disease, joint pain associated with transient regional osteoporosis, joint pain associated with neuropathic arthropathy, joint pain associated with sarcoidosis, arthritic joint pain, rheumatic joint pain, acute pain, acute joint pain, chronic pain, chronic joint pain, inflammatory pain, inflammatory joint pain, mechanical pain, mechanical joint pain, pain associated with the fibromyalgia syndrome (FMS), pain associated with polymyalgia rheumatica, monarticular joint pain, polyarticular joint pain, nociceptive pain, psychogenous pain, pain of unknown etiology, pain mediated by IL-6, IL-6 soluble receptor, or IL-6 receptor, pain associated with a surgical procedure in a patient with a clinical diagnosis of OA, pain like static allodynia, pain like dynamic allodynia, pain associated with Crohn's disease, and/or pain associated with completion of a large number of patent applications within a limited interval of time.

Generally, the frequency of administration of a particular dosage form is determined to provide the most effective results in an efficient manner without overdosing and varies according to the following criteria: (1) the characteristics of the particular drug(s), including both its pharmacological characteristics and its physical characteristics, such as solubility; (2) the characteristics of the swellable matrix, such as its permeability; and (3) the relative amounts of the drug and polymer. In most cases, the dosage form is prepared such that effective results are achieved with administration once every eight hours, once every twelve hours, or once every twenty-four hours. As previously discussed, due to the physical constraints placed on a tablet or capsule that is to be swallowed by a patient, most dosage forms can only support a limited amount of drug within a single dosage unit.

In one embodiment, the dosage form allows a dosing frequency of two times a day (b.i.d.) or three times a day (t.i.d.) to result in sustained plasma concentration of both drugs as compared to current immediate release products which require more frequent administration for effective sustained pain relief.

Within the context of the present disclosure, the gastric retentive dosage forms have the advantage of improving patient compliance with administration protocols because the drugs may be administered in a once-daily or twice-daily dosing regimen, rather than the multiple dosing administrations necessary for the immediate release dosage forms of

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acetaminophen and/or opioids in order to maintain a desired level of pain relief. One embodiment of the invention relates to a method of administering a therapeutically effective amount of a combination of acetaminophen and an opioid to a patient in need thereof, comprising administering the acetaminophen and opioid or pharmaceutically acceptable salts thereof, in a gastric retentive dosage form once in the morning or evening in a once a day daily regime. Another embodiment comprises administering the gastric retentive dosage form twice a day, for example once in the morning and once in the evening in a twice a day daily dosage regime.

For all modes of administration, the gastric retentive dosage forms described herein are preferably administered in the fed mode, i.e., with or just after consumption of a small meal (see U.S. Publication No. 2003/0104062, herein incorporated by reference). When administered in the evening fed mode, the gastric retentive dosage form may provide the subject with continued relief from pain through the night and into the next day. The gastric retentive dosage form of the present invention is able to provide pain relief for an extended period of time because the dosage form allows for both extended release of the acetaminophen and opioid and the superior absorption of the drugs in the GI tract.

In some aspects, the postprandial or fed mode can also be induced pharmacologically, by the administration of pharmacological agents that have an effect that is the same or similar to that of a meal. These fed-mode inducing agents may be administered separately or they may be included in the dosage form as an ingredient dispersed in the shell, in both the shell and the core, or in an outer immediate release coating. Examples of pharmacological fed-mode inducing agents are disclosed in U.S. Pat. No. 7,405,238, entitled "Pharmacological Inducement of the Fed Mode for Enhanced Drug Administration to the Stomach," inventors Markey, Shell, and Berner, the contents of which are incorporated herein by reference.

EXAMPLES

The following examples illustrate certain aspects and advantages of the subject matter, however, the present invention is in no way considered to be limited to the particular embodiments described below.

Example 1

Acetaminophen (APAP) and Phenylephrine (PE) Combination Formulations

Dosage forms were made using an phenylephrine HCl ("PE") model. Phenylephrine is highly soluble in water (500 mg/ml) with a molecular weight (203.67 Daltons (Da)). This solubility is of the same order of magnitude as the above mentioned opioids in a similar molecular weight range (approximately 350 to 450 Da) with similar dose strength and dose range on a milligram basis.

Four formulations for the production of extended release 960 mg tablets comprising acetaminophen (APAP), phenylephrine (PE) and a swellable polymer were manufactured using a dry blend process, and hand made on a Carver Auto C Press (Fred Carver, Inc., Indiana). The formulations also included polyvinylpyrrolidone (PVP) and magnesium stearate. In formulations (samples) 3 and 4, microcrystalline cellulose (MCC) was also added. The dry blend process consisted of blending all the ingredients in a glass jar, and compressing into a 960 mg tablet using a 0.3937"x0.7086" Modified Oval die (Natoli Engineering, St. Charles, Mo.).

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The parameters for the operation of the carver Auto C Press were as follows: 3000 lbs force, 0 second dwell time (the setting on the Carver Press), and 100% pump speed. Samples 1 and 2 contain 650 mg acetaminophen and 30 mg phenylephrine. Samples 3 and 4 contain 500 mg acetaminophen and 30 mg phenylephrine. The formulations for the tablets are set forth below in Tables 1-4:

TABLE 1

FORMULATION COMPOSITION (wt %)					
Sample No.	APAP	PE	PVP	PEO N-60K	Mg Stearate
1	67.71	3.13	3.88	24.28	1

TABLE 2

FORMULATION COMPOSITION (wt %)					
Sample No.	APAP	PE	PVP	PEO 1105	Mg Stearate
2	67.71	3.13	3.88	24.28	1

TABLE 3

FORMULATION COMPOSITION (wt %)						
Sample No.	APAP	PE	PVP	PEO N-60K	MCC	Mg Stearate
3	52.08	3.13	3.88	24.22	16.60	1

TABLE 4

FORMULATION COMPOSITION (wt %)						
Sample No.	APAP	PE	PVP	PEO 1105	MCC	Mg Stearate
4	52.08	3.13	2.97	24.22	16.60	1

Gastric retentive acetaminophen (APAP) and phenylephrine (PE) combination 1000 mg tablets were manufactured using a dry blend process, and hand made on a Carver Auto C Press (Fred Carver, Inc., Indiana). The dry blend process consisted of blending all the ingredients in a glass jar, and compressing into a 1000 mg tablet (650 mg APAP and 30 mg PE dose) using a 0.3937"x0.7086" Modified Oval die (Natoli Engineering, St. Charles, Mo.). The parameters for the operation of the carver Auto C Press were as follows: 3000 lbs force, 0 second dwell time (the setting on the Carver Press), and 100% pump speed. The formulations for the tablets are set forth in Table 9:

TABLE 5

FORMULATION COMPOSITION (wt %)					
Sample No.	APAP	PE	MCC	PEO N-60K	Mg Stearate
5	65	3	0	31	1
6	0	3	65	31	1
7	65	0	3	31	1

The dissolution profiles for the above samples 1-7 were determined in USP apparatus (40 mesh baskets), 100 rpm, in pH 5.8 phosphate buffer. Samples of 5 ml at each time-point, were taken without media replacement at 1, 2, 4, 6, 8 and 12 hours. The resulting cumulative dissolution profiles for

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samples 1-4, based upon a theoretical percent active added to the formulations, are set forth in Tables 6 and 7 below.

TABLE 6

THEORETICAL wt % OF ACTIVE RELEASED				
TIME (HOURS)	SAMPLE 1		SAMPLE 2	
	APAP	PE	APAP	PE
1	34.0	26.5	22.1	33.6
2	42.5	39.5	32.1	46.5
4	53.8	56.4	46.8	64.5
8	68.4	76.2	66.8	86.4
12	79.0	87.5	80.4	97.6

TABLE 7

THEORETICAL wt % OF ACTIVE RELEASED				
TIME (HOURS)	SAMPLE 3		SAMPLE 4	
	APAP	PE	APAP	PE
1	10.9	28	11.4	33.7
2	18.3	39.5	21.4	47.7
4	31.1	55.3	38.5	66.3
8	66.5	87.1	79.3	97.7
12	51.5	75.3	62.6	87.3

The cumulative dissolution release profiles of formulation samples 1-4 are shown in FIG. 1-FIG. 4.

The cumulative dissolution profiles for 5, 6 and 7, based upon a theoretical percent active added to the formulations is set forth in Table 8:

TABLE 8

THEORETICAL wt % OF ACTIVE RELEASED				
TIME (HOURS)	SAMPLE 5		SAMPLE 6	
	APAP	PE	PE	APAP
1	11	31.5	21.9	11.7
2	18	44.2	34.4	18.9
4	30	61.3	53.9	30.8
8	49	82.1	77.4	49.5
12	64.6	94	90.2	64.6

The cumulative dissolution release profiles of samples 5, 6 and 7 are shown in FIG. 5.

The disintegration was determined in USP Disintegration Tester in pH 5.8 phosphate buffer. Samples, 1 ml at each time-point, were taken without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profile, based upon a theoretical percent active added to the formulation is set forth in Tables 7 and 8 below.

TABLE 9

THEORETICAL wt % OF ACTIVE RELEASED				
TIME (HOURS)	SAMPLE 1		SAMPLE 2	
	APAP	PE	APAP	PE
0.5	31.0	21.2	18.5	26.7
1	38.1	31.7	28.5	38.8
2	48.3	47.1	44.6	57.4
3	57.2	59.9	58.4	72.0
4	66.3	72.4	70.9	85.3

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TABLE 9-continued

TIME (HOURS)	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 1		SAMPLE 2	
	APAP	PE	APAP	PE
5	73.5	81.5	79.3	93.2
6	81.5	90.3	86.0	98.2
7	87.3	95.5	91.4	100.5
8	91.5	97.6	93.3	100.6

TABLE 10

TIME (HOURS)	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 3		SAMPLE 4	
	APAP	PE	APAP	PE
1	14.8	29.4	20.9	36.4
2	27.2	43.1	39.9	54.4
4	51.1	65.5	68.7	78.9
6	73.0	82.9	85.8	91.1
8	89.5	93.0	93.3	92.6

The disintegration release profiles of samples 1-4 are shown in FIG. 6-FIG. 9.

Phenylephrine (PE) release profiles vs. square root of time (SQRT (T)) in samples 1-4 are shown in FIG. 10 and FIG. 11, respectively. The graphs show that PE release mechanism in the samples are the mixture of diffusion and erosion. The PE release profiles vs. the square root of time for samples 1 and 2 are shown in FIG. 10. The PE release profiles vs. the square root of time for samples 3 and 4 are shown in FIG. 11.

The use of the higher molecular weight polyethylene oxide N60K resulted in a slower rate of release as compared to the use of polyethylene oxide 1105 (for example, compare FIG. 1 and FIG. 2 and compare FIG. 3 and FIG. 4). Adding microcrystalline cellulose to the formulation having 500 mg acetaminophen and polyethylene oxide N60K resulted in a slower release of acetaminophen as compared to the release of phenylephrine (for example, compare FIG. 1 and FIG. 3 and compare FIG. 6 and FIG. 8).

Example 2

Acetaminophen and Oxycodone Hydrochloride Extended Release Gastric Retentive Formulations

An extended release matrix comprising acetaminophen, oxycodone hydrochloride and one of two poly(ethylene oxide) polymers (POLYOX®) was manufactured using a fluid bed granulation process followed by screening, blending and compression. Each formulation was prepared in a batch (lot) of 1000 g and contained 42.3 to 42.4 wt % acetaminophen, 2.3 to 2.4 wt % oxycodone hydrochloride, and 1.4 wt % povidone USP (K-29/32). After the granulation, the API granules were screened through USP #20 mesh screen, and blended with various amount of two different grades of POLYOX®, microcrystalline cellulose (Avicel PH 101 NF), and Magnesium Stearate, NF. The blend was then compressed into tablets and ready for analysis. Each batch varied in the amount and type of polymer present. Table 11 below shows the formulation of each batch with POLYOX® 1105 and POLYOX® N60K. Amounts of microcrystalline cellulose (Avicel® PH 101) were varied based on the amounts of the polymer.

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TABLE 11

Lot Number	Polymer (wt/wt %)	Polymer (mg/tablet)	Micro-crystalline Cellulose (wt/wt %)	Micro-crystalline Cellulose (mg/tablet)
			(wt/wt %)	(mg/tablet)
5 081104-01	POLYOX® 1105 (20%)	142.8 mg	(32.9%)	235.3 mg
10 081104-02	POLYOX® 1105 (32%)	228.8 mg	(20.9%)	149.4 mg
081104-03	POLYOX® 1105 (50%)	356.3 mg	(3.2%)	23.1 mg
15 081104-04	POLYOX® N60K (10%)	72.0 mg	(42.9%)	306.5 mg
081104-05	POLYOX® N60K (32%)	229.0 mg	(20.9%)	149.4 mg
20 081104-06	POLYOX® N60K (45%)	322.0 mg	(7.9%)	56.4 mg

Batches (lots) of 1 kg each were prepared for each formulation. For each formulation, the acetaminophen was sprayed with a 8.0-8.5% weight/weight solution of povidone and oxycodone hydrochloride in water in a fluid bed granulator (GLATT® top spray GPCG1). Fluid bed process parameters including spray rate (10-30 g/ml), inlet air temperature (50-70° C.), and fluidized air volume were varied to maintain the granule product temperature at a range of 28-35° C. Atomization air pressure was maintained at 1.5 bar for the entire granulation process. Granules were dried and blended with the polymer, filler and lubricant using a V-blender (PK blender, Patterson-Kelly Harsco). The polymer and filler were first blended for 10-15 minutes, the lubricant was then added, and blending was continued for another 4 minutes.

Tablets were then prepared using a Manesty® Beta press, tooled with a modified oval 0.3937" width×0.6299" length×0.075" cup depth die. A compression force of 7-13 kN (kilo Newton) was used, with a speed of 1000-2200 tablets/min.

Disintegration profiles for the tablets produced from the six batches described above were determined in USP Disintegration Tester in pH 1.2, 0.1N HCl at 37±2° C. Samples were taken without media replacement at 1, 2, 4, 6, 7 and 8 hours.

Results of the disintegration tests for the tablets having the formulations set forth in Table 11 are presented in Table 12 (cumulative oxycodone hydrochloride release) and 13 (cumulative acetaminophen release). Graphical representation of the data is provided in FIG. 12-FIG. 13.

TABLE 12

(Cumulative Oxycodone Hydrochloride Release)						
Time (hr)	Lot 081104-01	Lot 081104-02	Lot 081104-03	Lot 081104-04	Lot 081104-05	Lot 081104-06
1	55	31	25	67	26	22
2	72	51	43	84	40	36
3	98	85	76	103	67	61
6	111	106	104	—	94	88
7	—	—	106	—	100	96
8	—	—	—	—	106	105

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TABLE 13

(Cumulative Acetaminophen Release)						
Time (hr)	Lot 081104-01	Lot 081104-02	Lot 081104-03	Lot 081104-04	Lot 081104-05	Lot 081104-06
1	50	24	17	63	18	14
2	68	45	35	81	32	27
3	96	80	71	107	60	52
6	114	107	106	—	90	81
7	—	108	110	—	98	92
8	—	—	—	—	106	104

The results clearly show that release depends at least in part upon the molecular weight of the poly(ethylene oxide) polymer, the percent composition of the polymer, and the amount of microcrystalline cellulose in the formulation. The cumulative release of oxycodone hydrochloride is presented in FIG. 12, which shows that approximately 20-55% of the oxycodone hydrochloride was released from the tablets containing POLYOX® 1105 within the first hour. The cumulative release profiles of oxycodone hydrochloride from tablets having POLYOX® N60K, shows that approximately 20-65% of the oxycodone hydrochloride was released from the tablets within the first hour. Extended release approaching zero-order was observed over a period of approximately 6 hours for the tablets containing POLYOX® 1105, while tablets containing 32% or 45% POLYOX® N60K exhibited approximately zero-order release over a period of approximately 8 hours.

The acetaminophen cumulative release profiles for the same dosage forms are presented in FIG. 13, which shows that a range of approximately 20-50% of the acetaminophen was released from the tablets containing POLYOX® 1105 in the first hour, while the cumulative release profiles of acetaminophen from tablets having POLYOX® N60K, show that approximately 15-65% of the acetaminophen was released from the tablets within the first hour. The tablets containing 32% or 45% POLYOX® N60K exhibited extended release approaching zero-order over a period of approximately 8 hours, as seen with the oxycodone hydrochloride.

Linear regression of data presented in FIG. 12-13 was performed for lots 08110403 (50% POLYOX® 1105) and 08110406 (45% POLYOX® N60K) as shown in FIG. 14 and FIG. 15, respectively. It was determined that oxycodone hydrochloride was released from the tablets having 50% POLYOX® 1105 at a linear rate of approximately 2.8 mg/h while the acetaminophen was released at a rate of approximately 48 mg/h.

Linear regression of cumulative release data for lot 08110406 (45% POLYOX® N60K) show that oxycodone hydrochloride was released from the tablets at a linear rate of approximately 2.1 mg/h while the acetaminophen was released at a rate of approximately 36.8 mg/h.

Content uniformity analysis of lots 08110403 and 08110406 was done by analyzing five tablets from each batch. Each tablet was weighed then transferred to a 250 mL volumetric flask to which 200 mL 0.1N HCl was added. The flask was then set on a magnetic stirrer, a magnetic stir bar was put into the flask and the solution was stirred at approximately 1000 rpm overnight at room temperature, until all fragments had visibly dissolved. Additional 0.1N HCl was then added to the flask to a final volume of 250 mL and stirred for an additional 30 minutes. One mL of each solution for each tablet was placed into a separate flask and diluted with mobile

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phase solution (97% water/3% IPA/0.1% TFA, apparent pH=3.0±0.1) for analysis on a Agilent 1100/1200 HPLC system.

The resultant data are shown in Tables 14 and 15, respectively. For tablets containing 50% POLYOX® 1105, content uniformity with respect to oxycodone hydrochloride ranged from 91.0% to 92.4% of the label claim, with a mean of 91.6% and a standard deviation of 0.7. Content uniformity with respect to the acetaminophen ranged from 98.5% to 100.5% of the label claim with a mean of 99.4% and a standard deviation of 0.9.

For tablets containing 45% POLYOX® N60K, content uniformity with respect to oxycodone hydrochloride ranged from 91.0% to 95.2% of the label claim, with a mean of 91.6% and a standard deviation of 0.7. Content uniformity with respect to the acetaminophen ranged from 99.2% to 103.1% of the label claim with a mean of 99.4% and a standard deviation of 0.9.

TABLE 14

(Content Uniformity for Oxycodone Hydrochloride)		
Lot Number	APAP % LC (304 mg)	OXY % LC (16 mg)
08110403-1	100.5	92.4
08110403-2	98.8	91.2
08110403-3	98.5	91.0
08110403-4	100.2	92.3
08110405-5	99.1	91.2
Mean	99.4	91.6
Std Dev	0.9	0.7
% RSD	0.9	0.7

TABLE 15

(Content Uniformity for Acetaminophen)		
Lot Number	APAP % LC (304 mg)	OXY % LC (16 mg)
08110406-1	99.2	91.0
08110406-2	101.9	93.6
08110406-3	103.1	95.2
08110406-4	101.5	93.4
08110406-5	99.9	91.9
Mean	101.1	93.0
Std Dev	1.6	1.6
% RSD	1.5	1.8

Tablets were tested for hardness using a Venkel Tablet Tester according to standard USP protocol. Tablet hardness ranged from 9-12 kp.

Example 3

An immediate release composition having acetaminophen and oxycodone hydrochloride was produced using the methods described herein. The formulation is presented in Table 16 below.

TABLE 16

Ingredient	% wt/wt	Mg/Tablet
Acetaminophen	71.3	233.2 mg
Oxycodone hydrochloride	4.9	16.0 mg
Povidone, NF (Plasdone, K29/32)	9.2	30.1
Croscarmellose Sodium,	1.7	5.6

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TABLE 16-continued

Ingredient	% wt/wt	Mg/Tablet
NF (Ac-Di-Sol)		
Lactose Monohydrate, NF (316 Fast Flow)	6.0	19.6
Microcrystalline Cellulose, NF (Avicel PH-101)	6.0	19.6
Magnesium Stearate NF (Non-bovine)	0.9	2.9
Total weight		327.0

A mixture containing the acetaminophen, croscarmellose sodium, lactose monohydrate, and microcrystalline cellulose was sprayed with a solution containing the oxycodone hydrochloride and povidone (approximately 9%) in water in a fluid bed granulator (Vector® top spray FLM1). The granules were then screened through a USP #20 mesh screen. The resultant granules were blended with magnesium stearate in a V-blender (PK blender, Patterson-Kelly Harsco) for 4 minutes, and were then ready for bilayer compression.

Example 4

Bilayer tablets containing the extended release polymer matrix and the immediate release component (Example 3) were prepared using a Manesty® BB4 press, tooled with a modified oval 0.4337" widthx0.7450" length die. The formulation for the extended release material used in the compression is presented in Table 17 below.

TABLE 17

Ingredient	% wt/wt	Mg/Tablet
Acetaminophen	41.9	300.0 mg
Oxycodone hydrochloride	2.6	18.8 mg
Polyethylene oxide, NF (SENTRY™ POLYOXY™ WSR N 60K, LEO)	45.0	321.8
Povidone, NF (Plasdone, K29/32)	3.5	25.0
Microcrystalline Cellulose, NF (Avicel PH-101)	6.0	43.0
Magnesium Stearate NF (Non-bovine)	1.0	7.2
Total weight		715.0

The bilayer tablets were then characterized with respect to cumulative drug release using the USP Disintegration test at 37±2° C. in 0.1N HCl. Results, presented in Table 18 and illustrated in FIG. 16, show that approximately 50-55% of the acetaminophen had been released at the first time point of 1 hour, while approximately 55-57% of the oxycodone hydrochloride had been released by this time. This is indicative of drug release by the immediate release layer. Proportional release of acetaminophen and oxycodone hydrochloride was observed over a period of 8 hours.

TABLE 18

Time Point (hours)	Cumulative Acetaminophen Released (%)	Cumulative Oxycodone Hydrochloride Released (%)
1	53.2	57.2
2	62.6	67.0
4	77.6	83.0
6	88.2	95.8

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TABLE 18-continued

Time Point (hours)	Cumulative Acetaminophen Released (%)	Cumulative Oxycodone Hydrochloride Released (%)
7	92.7	100.9
8	96.1	105.1

The bilayer tablets were further characterized with respect to content uniformity. Five tablets were analyzed and the results, presented in Table 19, show that content uniformity ranged from 121.8 to 125.2% of the label claim for acetaminophen and ranged from 110.5 to 113.5% for oxycodone HCl. The standard deviation of the acetaminophen and oxycodone HCl were each 1.3, demonstrating that there is very little variation among the tablets with respect to the milligrams of acetaminophen and oxycodone HCl present in the tablets.

TABLE 19

C.U. Results	APAP % LC	Oxy % LC
1	124.5	113.0
2	121.8	110.5
3	125.2	113.5
4	123.7	111.5
5	123.0	111.1
Ave.	123.6	111.9
Std. Dev.	1.3	1.3
% RSD	1.1	1.1

Example 5

Bilayer tablets were also prepared using a high shear granulation method. A 5 kg batch was prepared for the gastric retentive extended release mixture and for the immediate release component mixture. The extended release layer contained 42.9% acetaminophen, 2.4 wt % oxycodone hydrochloride, 2.7 wt % povidone, 45.0 wt % POLYOX® N60K, 6.0 wt % microcrystalline cellulose, and 1.0 wt % magnesium stearate. The immediate release layer contained 77.5 wt % acetaminophen, 5.2 wt % oxycodone hydrochloride, 4.0 wt % povidone, 3.0 wt % croscarmellose sodium, 9.2 wt % microcrystalline cellulose, and 0.9 wt % magnesium stearate.

Granules for the extended release layer were prepared by high shear granulation using water as the granulating liquid. The acetaminophen, oxycodone hydrochloride and povidone were charged into a bench scale high shear granulator (Glatt®). The dry powders were blended by running the blade for 1 minute, after which time the water was sprayed onto the mixing blend at a spray rate of approximately 5-30 gm/min. After initiating the spray, the chopper was started and run throughout the spray. Once the granulation was complete, the granulation was discharged from the high shear granulator, and dried using a fluid bed processor (Glatt® top spray GPCG1). Dry granules were screened through an 20-mesh USP screen. Screened granules were blended with the remaining excipients except magnesium stearate in a V-blender (PK blender, Patterson-Kelly Harsco) for 15 minutes. The magnesium stearate was then added to the mixture and blended for another 4 minutes, and ready for bi-layer compression.

Granules for the immediate release layer were prepared using the high shear method as described above for the extended release layer. The acetaminophen, oxycodone hydrochloride, povidone, croscarmellose sodium, and microcrystalline cellulose were granulated using the high shear method prior to blending with magnesium stearate. Granules

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were screened through USP #20-mesh screen before blending with magnesium stearate. After blending, they were ready for bi-layer compression.

The extended release and immediate release blends were compressed into bilayer tablets using a hand roll method with a Manesty® Beta BB4 press, tooled with a modified oval 0.4337" width×0.7450" length die.

The bilayer tablets prepared by high shear granulation were characterized with respect to cumulative drug release using the USP Disintegration test at 37±2° C. in 0.1N HCl. Results are presented in FIG. 17 and show that approximately 50% of the acetaminophen had been released at the first time point of 1 hour, while approximately 50% of the oxycodone HCl had been released by this time. This is indicative of drug release by the immediate release layer. Proportional release of acetaminophen and oxycodone HCl was observed over a period of approximately 8 hours.

The bilayer tablets were further characterized with respect to content uniformity. Five tablets were analyzed and the results, presented in Table 20, show that content uniformity ranged from 99.1% to 101.9% of the label claim for acetaminophen and ranged from 98.6% to 101.4% for oxycodone HCl. The standard deviation for acetaminophen and oxycodone HCl was 1.2 and 1.3, respectively. Both values dem-

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TABLE 21

Ingredients	% w/w	mg/tablet
APAP, USP Powder	41.9	299.9
Tramadol HCl	2.6	18.8
Povidone, USP (K-29/32)	3.4	24.5
POLYOX, NF (N60K)	45.0	321.8
Avicel, NF (PH 101)	6.0	43.0
Mg Stearate, NF	1.0	7.2
Total tablet weight		715 mg

Fluidized bed granulation was performed on Vector FL-M-1 Fluid Bed Granulator. The acetaminophen was sprayed with a binder solution containing the PVP and the tramadol hydrochloride. After granulation, the resultant preparation was characterized with respect to final loss on drying (LOD), bulk density, and tap density.

The granulation parameters and post-granulation characterization are presented below in Table 22.

TABLE 22

		09011201	09012001	09012101	09012201	09012202
Granulation	Batch size (g)	1000	1000	1000	1000	1000
	Inlet air temp (° C.)	56	53-56	52-56	50-58	51-58
	Product temp at spray start (° C.)	30	32	31	30	31
	Product temp during spray (° C.)	30-38	31-34	30-34	30-36	30-34
	Spray rate (rpm)	15-20	12-20	12-20	12-20	12-20
	Spraying time (min)	29	23	22	23	24
	Product temp during drying (° C.)	36-42	34	34-35	37-38	37-38
	Drying time (min)	3	1	1	1	1
Post-gran	Final LOD (%)	1.47	1.66	1.69	1.38	1.75
	Bulk Density (g/ml)	0.35	0.30	0.30	0.33	0.31
	Tap Density (g/ml)	0.41	0.37	0.37	0.40	0.39

onstrate very low levels of variability among individual tablets with respect to the milligrams of acetaminophen and oxycodone HCl present in the tablets.

Machine production of the bilayer tablets using the Manesty® Beta BB4 press tooled with a modified oval 0.4337" width×0.7450" length die resulted in tablets in which the IR layer was subject to capping.

TABLE 20

C.U. Results	APAP % LC	Oxy % LC
1	99.1	99.2
2	99.2	98.6
3	101.1	101.4
4	101.9	101.4
5	99.1	98.6
Ave.	100.1	99.8
Std. Dev.	1.2	1.3
% RSD	1.2	1.3

Example 6

An extended release matrix comprising acetaminophen, tramadol hydrochloride and 45% POLYOX® N60K was manufactured using a fluid bed granulation process followed by screening, blending and compression as described in Example 2. The formulation is shown in Table 21 below:

The granulation mixture was then screened and blended with the remaining excipients in a V blender and compressed into tablets.

The particle size distribution of the blend was determined using a particle size shaker with a timer (W.S. Tyler Inc., ROTAP, RX-29) and U.S. standard sieve series: No. 60 (250 µm), 100 (150 µm), 140 (106 µm), 200 (75 µm), 270 (53 µm) and 325 (45 µm). Fifty grams of sample was accurately weighed and transferred to the top sieve, then the shaker was allowed to shake for 5 minutes. The material remaining on the top of each sieve was then weighed to the nearest 0.1 gram. The results are provided in Table 23 below and shown in FIG. 18.

TABLE 23

Sieve size (µm)	Lot 09011201	Lot 09012001	Lot 09012101	Lot 09012201	Lot 09012202
250	57.0	61.4	57.4	53.9	60.0
150	30.0	21.7	23.6	26.4	21.0
106	8.0	7.6	11.0	9.3	8.0
75	3.0	4.2	4.8	4.8	5.0
53	2.0	3.0	3.2	5.4	5.0
44	0	1.2	1.2	0.2	0
Fines	0.6	0.8	0.8	0.0	0

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An immediate release matrix comprising acetaminophen and tramadol was then produced having the formulation presented in Table 24.

TABLE 24

Ingredients	% wt/wt
Acetaminophen USP Powder	0.30
Tramadol HCl	4.80
Povidone USP (K-29/32)	9.00
AcDiSol	3.00
Lactose	6.45
Avicel PH101	6.45

Fluidized bed granulation was performed on Vector FL-M-1 Fluid Bed as described for the gastric retentive matrix. A binder solution of povidone and the tramadol was sprayed onto the acetaminophen. The granules were then blended with the remaining excipients. The granulation properties and the post-granulation characterization of the IR matrix are presented below in Table 25.

TABLE 25

	09010502	09010901	09010902	09011301	09011502	09011503
Batch size (g)	600	1000	1000	1000	1000	1000
Inlet air (° C.)	50-51	49-51	51-58	51-58	49-53	47-49
Product temp at spray start (° C.)	35	31	36	35	31	30
Product temp during spray (° C.)	32-38	28-31	33-38	33-36	29-35	29-32
Spray rate (rpm)	7-15	8-19	8-20	8-19	8-19	8-19
Spraying time (min)	22	25	37	36	37	37
Product temp during drying (° C.)	32-40	41	36-39	35-37	34-35	32-34
Drying time (min)	3	5	2	2	2	2
Final LOD (%)	1.8	1.03	1.43	1.6	1.95	2.19
Bulk Density (g/ml)	N/M	0.39	0.29	0.32	0.32	0.31
Tap Density (g/ml)	N/M	0.45	0.34	0.38	0.40	0.38
Carr Index	N/M	15	16	16	20	18

Compression of the gastric retentive extended release matrix with the immediate release matrix produced above was done using a Manesty® BB4 press, at a compression speed of 220 tablets per minute, tooled with a modified oval 0.4337" width×0.7450" length die.

A comparison of segments of data from a 12 minute run of the tablet press showed that the resultant tablets had a friability ranging from 0.01 to 0.12 and did not split during hardness testing. The comparison data are summarized in Table 26 below.

TABLE 26

Section	Beginning	Middle	End
Compression			
Compression speed (rpm)	32	32	32
Avg tablet weight (g)	1.019 ± 0.018	1.012 ± 0.016	0.992 ± 0.033
Avg tablet hardness (kp)	19.6 ± 1.1	18.9 ± 1.4	17.2 ± 2.5
2 nd compression force (N)	9.8	11.7	9.1
Avg tablet thickness (mm)	7.8 ± 0.03	7.8 ± 0.03	7.8 ± 0.04
Tablets split during hardness testing (%)	0	0	0
Friability (%)	0.12	0.03	0.01
	Samples from bag 1/6	Samples from bag 4/6	Samples from bag 6/6

Example 7

A bilayer tablet with first and second doses of acetaminophen and tramadol, comprising a gastric retained extended release layer and an immediate release layer, and having a total weight of 1042 mg, was made according to the formu-

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lations presented in Table 27 (extended release) and Table 28 (immediate release). To prepare the extended release layer, methods described in Example 2 were used. The acetaminophen, the tramadol and the binder were first wet granulated using the fluid bed granulation described in Example 2. The resultant granulation mixture was then screened and blended with the polymer, filler, color agent, and lubricant in a V-blender.

To prepare the immediate release layer, methods described in Example 3 were used. All ingredients except magnesium stearate were wet granulated using the fluid bed granulation method, the granules were then screened and blended with lubricant in a V-blender then ready for compression.

The extended release component and the immediate release component was then compressed into a bilayer tablet using a Manesty BB4 press, tooled with a modified oval 0.4337" width×0.7450" length die. A compression force of 7-13 kN (kilo Newton) was used, with a speed of 1000-2200 tablets/min.

TABLE 27

Ingredient	Function	wt %	Mg/tablet
Acetaminophen	active agent	41.9	299.9
Oxycodone	active agent	2.6	18.8
Hydrochloride			
Povidone, NF	binder	3.4	17
(Plasdone, K29/32)			
Polyethylene oxide,	swellable and	45.0	321.8

TABLE 27-continued

Ingredient	Function	wt %	Mg/tablet
NF (Sentry™	release-controlling		
POLYOX™ WSR	polymer		

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TABLE 27-continued

Ingredient	Function	wt %	Mg/tablet
N60K, LEO Microcrystalline cellulose, NF (Avicel PH-101)	Filler	5.8	41.5
Opadry ® blue	color agent	0.2	1.5
Magnesium stearate, NF (non-bovine)	lubricant	1.0	7.2
Total		100.0	715.0

TABLE 28

Ingredient	Function	wt %	Mg/tablet
Acetaminophen	active agent	70.1	229.3
Oxycodone	active agent	4.8	15.7
Hydrochloride			
Povidone, NF (Plasdone, K29/32)	binder	9.0	29.4
Croscarmellose sodium, NF (Ac-Di-Sol)	disintegrant	3.0	9.8
Microcrystalline cellulose, NF (Avicel PH-101)	Filler	6.4	21.0
Lactose monohydrate, NF (316 Fast Flow)	Compression-aid	6.4	21.0
Magnesium stearate, NF (non-bovine)	lubricant	0.3	0.8
Total		100.0	327.0

Disintegration profiles for the tablets produced from the six batches described above were determined in USP Disintegration Tester in pH 1.2 0.1N HCl at 37±2° C. Samples were taken without media replacement at 1, 2, 4, 6, 7 and 8 hours. Cumulative release values for acetaminophen and tramadol at the time points are presented in Table 29 below, and illustrated in the graph in FIG. 20. The data show proportional release rates for the acetaminophen and tramadol over a period of 7 hours.

TABLE 29

Active Ingredient	1 h	2 h	4 h	6 h	7 h	8 h
Acetaminophen	51.4	61.6	81.0	98.3	106.5	103.5
Tramadol	59.8	72.3	95.3	112.8	118.3	122.1

Content uniformity of the bilayer tablets was tested using the methods described in Example 2. As shown in Table 30 below, the average content uniformity based on weight for acetaminophen was 95.5% of the label claim, while the average content uniformity based on weight for tramadol was 101.0% of the label claim. Standard deviations for acetaminophen and tramadol were 3.1 and 4.1, respectively.

TABLE 30

Tablet	APAP, % LC (522.9 mg)	TRAM, % LC (37.7 mg)	APAP, % LC (base on wt)	TRAM, % LC (base on wt)
1	91.5	95.6	93.8	98.5
2	92.8	97.2	95.9	101.0

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TABLE 30-continued

Tablet	APAP, % LC (522.9 mg)	TRAM, % LC (37.7 mg)	APAP, % LC (base on wt)	TRAM, % LC (base on wt)
3	93.4	98.2	96.1	101.6
4	88.9	93.3	92.1	97.1
5	90.8	94.0	91.3	94.9
6	92.7	96.8	94.9	99.7
7	93.2	97.7	94.5	99.7
8	92.6	98.0	96.0	102.1
9	95.2	102.0	101.5	109.2
10	90.3	93.2	90.7	94.1
11	92.8	98.5	97.0	103.5
12	94.3	99.7	97.8	103.9
13	87.3	91.5	89.9	94.7
14	92.0	99.0	99.0	107.1
15	90.0	93.1	91.3	95.0
16	91.4	96.5	94.1	99.9
17	88.8	91.8	89.6	93.2
18	92.5	97.8	97.4	103.5
19	92.3	98.5	98.7	105.9
20	94.6	100.7	99.2	106.1
21	94.1	99.7	98.5	105.0
22	94.5	100.2	98.3	104.8
23	93.3	98.4	96.0	101.8
24	97.2	101.9	100.3	105.8
25	90.6	95.6	95.5	101.4
26	91.1	95.2	93.7	98.5
27	91.0	95.3	94.8	99.9
28	91.7	96.8	96.2	102.0
29	92.5	97.0	95.7	100.9
30	92.3	96.5	94.9	99.7
Ave.	92.2	97.0	95.5	101.0
Std. Dev.	2.1	2.8	3.1	4.1
% RSD	2.2	2.9	3.2	4.1

Example 8

A bilayer tablet comprising a gastric retained extended release layer and an immediate release layer is made containing the formulation presented in Table 31, in which the immediate release layer contained hydroxypropylcellulose (HPC) as the binder instead of PVP. The extended release layer contains PVP as the binder and was prepared as described in Example 2. The acetaminophen, the opioid and povidone (PVP) were first wet granulated using the fluid bed. The resultant granulation mixture was then blended with the polymer, filler, and lubricant in a V-blender. To prepare the immediate release layer, the acetaminophen, the opioid, and hydroxypropylcellulose (HPC) were first wet granulated using the fluid bed granulation. The resultant granulation mixture was then blended with the lubricant. The bilayer tablets were compressed on a Manesty BB4 machine using 0.4330" wide×0.7450 long modified oval tooling. The amounts of each component in the bilayer tablets is presented in Table 31. The dissolution release profile of acetaminophen and oxycodone HCl is shown in Table 32 and in FIG. 21 and FIG. 22.

TABLE 31

Ingredient	Function	wt %	Mg/tablet
Acetaminophen	active agent	50.88	500
Oxycodone Hydrochloride	active agent	3.05	30
Hydroxypropyl cellulose, NF (Klucel EF)	binder	2.88	28
Polyethylene Oxide, NF (Sentry™)	Swellable and release-controlling	28.73	282

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TABLE 31-continued

Ingredient	Function	wt %	Mg/tablet
POLYOX TM WSR N60K, LEO	polymer		
Povidone, NF (Plasdone, K29/32)	binder	1.53	15
Croscarmellose sodium, NF (Ac-Di-Sol)	disintegrant	1.08	11
Microcrystalline cellulose, NF (Avicel PH-101)	Filler	7.75	76
Lactose monohydrate, NF (316 Fast Flow)	Compression-aid	3.60	35
Magnesium stearate, NF (non-bovine)	lubricant	0.50	5
Total		100.0	982.0

TABLE 32

TIME (HOURS)	N = 6	
	APAP	Oxycodone
0.5	51.34154	53.25
1	54.83926	58.64767
2	60.27355	66.0131
4	69.5474	76.92073
6	77.73934	85.02003
8	84.23556	90.55967
12	93.07368	95.14833
13	94.74338	95.73057

Example 9

A bilayer tablet comprising a gastric retained extended release layer and an immediate release layer, having a total weight of 1042 mg, is made according to the formulations presented in Table 33 (extended release) and Table 34 (immediate release). To prepare the extended release layer, methods described in Example 2 are used. The acetaminophen, the opioid and the binder are first wet granulated using the fluid bed granulation described in Example 2. The resultant granulation mixture is then screened and blended with the polymer, filler, color agent, and lubricant in a V-blender.

To prepare the immediate release layer, methods described in Example 3 are used. All ingredients except magnesium stearate are wet granulated using the fluid bed granulation method, the granules are then screened and blended with lubricant in a V-blender then ready for compression.

The extended release component and the immediate release component are then compressed into a bilayer tablet using a Carver press, tooled with a modified oval 0.4850" width×0.7450" length modified Oval die. A compression force of 7-13 kN (kilo Newton) was used, with a speed of 1000-2200 tablets/min.

TABLE 33

Ingredient	Function	wt %	Mg/tablet
Acetaminophen	active agent	41.9	299.9
Oxycodone	active agent	2.6	18.8
Hydrochloride Povidone, NF (Plasdone, K29/32)	binder	3.4	17

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TABLE 33-continued

Ingredient	Function	wt %	Mg/tablet
Polyethylene oxide, NF (Sentry TM POLYOX TM WSR N60K, LEO	swellable and release-controlling polymer	45.0	321.8
Microcrystalline cellulose, NF (Avicel PH-101)	Filler	5.8	41.5
Opadry [®] blue	color agent	0.2	1.5
Magnesium stearate, NF (non-bovine)	lubricant	1.0	7.2
Total		100.0	715.0

TABLE 34

Ingredient	Function	wt %	Mg/tablet
Acetaminophen	active agent	70.1	229.3
Oxycodone	active agent	4.8	15.7
Hydrochloride Povidone, NF (Plasdone, K29/32)	binder	9.0	29.4
Croscarmellose sodium, NF (Ac-Di-Sol)	disintegrant	3.0	9.8
Microcrystalline cellulose, NF (Avicel PH-101)	Filler	6.4	21.0
Lactose monohydrate, NF (316 Fast Flow)	Compression-aid	6.4	21.0
Magnesium stearate, NF (non-bovine)	lubricant	0.3	0.8
Total		100.0	327.0

Example 10

A bilayer tablet containing a total of 500 mg acetaminophen and 15 mg oxycodone HCl designed for release of these active agents over 8 hours was manufactured using the wet granulation methods as described above using the formulations presented in Tables 35 and 36 for the ER and IR layers, respectively.

The extended release component and the immediate release component are then compressed into a bilayer tablet using a Manesty BB4 press, tooled with a modified oval 0.4337" width×0.7450" length die. A compression force of 1500 pounds was used, with a speed of 100% with a dwell time of 0.

TABLE 35

	wt %	mg/tablet
Acetaminophen	42.5	304.0
Oxycodone HCl	1.1	8.0
Povidone, NF (Plasdone, K29/32)	3.4	24.5
Polyethylene oxide, 301 NF LEO	45.0	321.8
Microcrystalline Cellulose, NF (Avicel PH-101)	3.9	28.1
Opadry [®] blue	3.0	21.5
Magnesium Stearate, NF (Non-Bovine)	1.0	7.2
Total	100.0	715.0

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TABLE 36

	wt %	mg/tablet
Acetaminophen	68.8	196.0
Oxycodone HCl	2.5	7.0
Povidone, USP (K29/32)	10.3	29.4
Ac-Di-Sol	3.4	9.8
Lactose	7.4	21.0
Avicel PH-101	7.4	21.0
Magnesium Stearate, NF	0.3	0.7
Total	100.0	284.9

The disintegration release profile of acetaminophen and oxycodone HCl formulated for acetaminophen and oxycodone release over 8 hours is provided in Table 37 and illustrated in FIG. 23.

TABLE 37

	Time Point (h)					
	1	2	4	6	7	8
Cumulative % APAP released	49.4	56.3	70.1	77.5	80.1	85.2
Std. Dev.	0.7	1.3	6.1	2.3	2.3	3.5
Cumulative % Oxy released	61.1	69.1	79.8	86.0	87.2	89.8
Std. Dev.	1.2	1.4	1.8	1.9	2.1	2.3

Example 11

A bilayer tablet containing a total of 500 mg acetaminophen and 15 mg oxycodone HCl formulated for release of the active pharmaceutical ingredients over 6 hours was manufactured as described above using the formulations presented in Tables 38 and 39 for the ER and IR layers, respectively.

TABLE 38

	wt %	mg/tablet
Acetaminophen	37.8	270.0
Oxycodone HCl	1.1	8.0
Povidone, NF (Plasdone, K29/32)	3.4	24.5
Polyethylene oxide, 301 NF LEO	45.0	321.8
Microcrystalline Cellulose, NF (Avicel PH-101)	8.7	62.1
Opadry ® blue	3.0	21.5
Magnesium Stearate, NF (Non-Bovine)	1.0	7.2
Total	100.0	715.0

TABLE 39

	wt %	mg/tablet
Acetaminophen	72.1	230.0
Oxycodone HCl	2.2	7.0
Povidone, USP (K29/32)	9.2	29.4
Ac-Di-Sol	3.1	9.8
Lactose	6.6	21.0
Avicel PH-101	6.6	21.0
Magnesium Stearate, NF	0.3	0.8
Total	100.0	319.0

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The disintegration release profile of acetaminophen and oxycodone HCl from the tablet formulation for release over 6 hours is provided in Table 40 and illustrated in FIG. 24.

TABLE 40

	Time Point (h)					
	1	2	4	6	7	8
Cumulative % APAP released	60.2	69.3	83.1	91.7	93.5	95.8
Std. Dev.	1.3	2.1	2.2	1.6	1.5	1.3
Cumulative % Oxy released	63.8	73.8	86.8	93.7	94.5	96.6
Std. Dev.	1.4	3.3	2.3	1.8	2.8	2.5

Example 12

A bilayer tablet containing a total of 500 mg acetaminophen and 30 mg oxycodone HCl designed for release over 8 hours was manufactured using the wet granulation methods as described above using the formulations presented in Tables 41 and 42 for the ER and IR layers, respectively.

The extended release component and the immediate release component are then compressed into a bilayer tablet using a Manesty BB4 press, tooled with a modified oval 0.4337" width×0.7450" length die. A compression force of 7-13 kN (kilo Newton) was used, with a speed of 1000-2200 tablets/min.

TABLE 41

	wt %	mg/tablet
Acetaminophen	42.5	304.0
Oxycodone HCl	2.2	16.0
Povidone, NF (Plasdone, K29/32)	3.4	24.6
Polyethylene oxide, 301 NF LEO	45.0	321.8
Microcrystalline Cellulose, NF (Avicel PH-101)	2.8	20.0
Opadry ® blue	3.0	21.5
Magnesium Stearate, NF (Non-Bovine)	1.0	7.2
Total	100.0	715.0

TABLE 42

	wt %	mg/tablet
Acetaminophen	67.1	196.0
Oxycodone HCl	4.8	7.0
Povidone, USP (K29/32)	10.1	29.4
Ac-Di-Sol	3.4	9.8
Lactose	7.2	21.0
Avicel PH-101	7.2	21.0
Magnesium Stearate, NF	0.25	0.7
Total	100.0	291.9

The disintegration release profile of acetaminophen and oxycodone HCl formulated for acetaminophen and oxycodone release over 8 hours is provided in Table 43 and illustrated in FIG. 25.

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TABLE 43

	Time Point (h)					
	1	2	4	6	7	8
Cumulative %	52.4	59.3	73.7	79.6	82.8	85.5
APAP released						
Std. Dev.	1.3	2.2	5.3	5.1	5.7	6.5
Cumulative %	69.9	75.3	84.1	89.9	91.2	93.0
Oxy released						
Std. Dev.	10.5	5.5	6.7	7.6	8.1	8.7

Example 13

A bilayer tablet containing a total of 500 mg acetaminophen and 30 mg oxycodone HCl formulated for release of the active pharmaceutical ingredients over 6 hours was manufactured as described above using the formulations presented in Tables 44 and 45 for the ER and IR layers, respectively.

TABLE 44

	wt %	mg/tablet
Acetaminophen	37.8	270.0
Oxycodone HCl	2.2	16.0
Povidone, NF (Plasdone, K29/32)	3.1	22.0
Polyethylene oxide, 301 NF LEO	45.0	321.8
Microcrystalline Cellulose, NF (Avicel PH-101)	7.9	56.7
Opadry® blue	3.0	21.5
Magnesium Stearate, NF (Non-Bovine)	1.0	7.2
Total	100.0	715.0

TABLE 45

	wt %	mg/tablet
Acetaminophen	70.6	230.0
Oxycodone HCl	4.3	14.0
Povidone, USP (K29/32)	9.0	29.4
Ac-Di-Sol	3.0	9.8
Lactose	6.4	21.0
Avicel PH-101	6.4	21.0
Magnesium Stearate, NF	0.3	0.8
Total	100.0	326.0

The disintegration release profile of acetaminophen and oxycodone HCl from the tablet formulation for release over 6 hours is provided in Table 46 and illustrated in FIG. 26. The release profiles indicate that both acetaminophen and oxycodone exhibit approximately zero-order release kinetics over about a 6 to 8 hour period. In vivo erosion studies of the dosage forms to demonstrate gastric retention of the tables are described in Examples 17-18.

TABLE 46

	Time Point (h)					
	1	2	4	6	7	8
Cumulative %	59.2	67.9	80.9	90.2	94.4	95.0
APAP released						
Std. Dev.	1.0	1.7	1.8	1.8	1.9	1.9
Cumulative %	69.7	79.8	93.3	101.0	104.7	104.4

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TABLE 46-continued

	Time Point (h)					
	1	2	4	6	7	8
Oxy released						
Std. Dev.	1.4	2.1	2.1	2.6	4.1	2.1

Example 13

Studies were done to evaluate the effect of the binder on the degradation rate of oxycodone in the presence of polyethylene oxide in the ER portion of the dosage form. Specifically, the use of HPC or PVP. Oxycodone HCl as well as a physical blend of acetaminophen and oxycodone HCl were tested ("Physical Blend"). Single layer ER tablets containing acetaminophen (APAP) and oxycodone HCl (Oxy) were formulated using the fluid bed granulation method described above. Specifically, the acetaminophen and oxycodone were granulated in the presence of either HPC or PVP as the binder. Granulated mixtures were then dried and pressed into tablets. Physical blends and tablets were then stored at 40° C., 75% relative humidity (RH) in an open dish for 8 days. Physical blends and tablets were analyzed for the presence of an unknown impurity and the ratio of the unknown purity to oxycodone (Oxy) was calculated. Physical blend and granules data are listed as an average of three individual sample preparations. Tablet data were obtained by analyzing one composite sample from five tablets.

The results are summarized in Table 47 and show that oxycodone HCl was more stable in tablets formulated with HPC as compared to PVP as the binder and suggest that it may be beneficial to formulate both the IR and ER layers of the dosage form using HPC rather than PVP as the binder.

TABLE 47

	DHOXY/OXY (%) ¹					
	Tablets ⁵					
	Physical Blend ⁴					
	40° C., 75% RH, open-dish					
	Polyox	t = 0	8 days	Granules ⁴	t = 0	8 days
Physical Blend						
Oxy only	NA	0.07	0.07	NA	NA	NA
APAP (500 mg)/Oxy (30 mg)	NA	0.02	0.10	NA	NA	NA
APAP/Oxy as a ER Single Layer						
APAP (304 mg) Oxy (16 mg) PVP (24.6 mg)	N60K			1.35	1.41	1.49
	301	NA	NA		1.23	1.47
APAP (304 mg) Oxy (16 mg) HPC (16.8 mg)	N60K					
	301	NA	NA	0.05	0**	0.07
	301	NA	NA		0.04**	0.37
MCC (160 mg) Oxy (16 mg) PVP (9.3 mg)	N60K					
	301	NA	NA	0.06	0.03	0.25
	301	NA	NA		0.11	0.26
APAP/Oxy IR/GR Bilayer	301	NA	NA	NA	0.78	1.30

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TABLE 47-continued

		DHOXY/OXY (%) ¹		Tablets ⁵	
Antioxidant	Polyox	Physical Blend ⁴		40° C.,	
		40° C., 75% RH, open- dish t = 0 8 days	Gran- ules ⁴ t = 0 8 days	40° C., 75% RH, open- dish t = 0 8 days	

(both IR and GR
have PVP as the
binder)

Example 14

Studies were done to evaluate the effect of antioxidants on the degradation rate of oxycodone in ER single layer tablets containing 500 mg acetaminophen and 30 mg oxycodone HCl which were high shear granulated with HPC as the binder. The antioxidant was added into the granulation process based on the maximum allowance level from the Inactive Ingredient Guide published by the FDA. The granules containing antioxidants were then blended with polyethylene oxide as described in previous examples. Samples were then stored at 40° C., 75% relative humidity (RH) in an open dish for 8 days, then analyzed. The results are presented below in Table 48 and show that the antioxidants citric acid, sodium metabisulfite, cysteine HCl reduce the degradation of oxycodone, thus suggesting that introducing antioxidant into the granulation process may be beneficial in minimizing degradation of the oxycodone or any opioid present in the dosage form.

TABLE 48

		DHOXY/OXY (%)		40° C., 75% RH, 8 days		Appearance
Antioxidant	Polyox	t = 0		RRT	%	
		RRT	%	RRT	%	
none	N60K	0.70	0.00	0.70	0.16	white to off-white
	301	0.70	NA	0.70	0.20	white to off-white
BHT	N60K	0.68	0.06	0.69	0.20	white to off-white
	301	0.72	0.05	0.70	0.20	white to off-white
Ascorbic Acid	N60K	0.71	0.07	0.71	0.94	brown
	301	0.71	0.06	0.71	0.97	brown
Citric Acid	N60K	0.72	0.05	0.72	0.04	slightly yellow
	301	0.72	NA	0.72	0.03	slightly yellow
Sodium Metabisulfite	N60K	0.72	0.02	0.72	0.05	white to off-white
	301	0.72	0.06	0.72	0.04	white to off-white*
Sodium Sulfite	N60K	0.70	NA	0.70	0.13	white to off-white
	301	0.72	0.03	0.72	0.04	white to off-white
Cystein HCl	N60K	0.72	0.04	0.72	NA	white to off-white
	301	0.68	NA	0.68	0.10	white to off-white

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TABLE 48-continued

		DHOXY/OXY (%)		40° C., 75% RH, 8 days		Appearance
Antioxidant	Polyox	t = 0		RRT	%	
		RRT	%	RRT	%	
	301	0.68	0.05	0.68	0.10	white to off-white
		0.72	NA	0.72	0.05	

*single yellow spat was observed randomly on some of the tablets.

Example 15

To produce oral dosage forms in which the oxycodone exhibits enhanced stability against oxidative degradation, a high-shear fluid bed granulation process was used in which the oxycodone HCl was granulated in the presence of pregelatinized starch, citric acid, microcrystalline cellulose, and EDTA disodium salt, dehydrate.

Powdered oxycodone HCl, microcrystalline cellulose (MCC), and citric acid powder (an antioxidant) were mixed together and charged into a high-shear granulator. An aqueous solution containing pregelatinized starch (PGS) and Na₂EDTA was sprayed into the high-speed granulator, resulting in the formation of wet granules. The wet granules were then dried until less than about 2% water remained in the granules. The dried granules had particle sizes ranging from about 100-300 µm. The composition of the protected oxycodone granules is summarized in Table 49.

TABLE 49

Compound	Dry Weight (% tot. wt.)
Oxycodone HCl	30.0%
MCC	63.6%
PGS	4.0%
Na ₂ EDTA	0.4%
Citric acid	2.0%

The protected oxycodone granules were divided into two groups to be incorporated into batches of instant release (IR) granules and into batches of extended release (ER) granules used to form the IR and ER layers of a bilayer tablet, respectively. Both the IR granules and the ER granules were formed using separate fluid bed granulation processes. In each process, the previously-formed protected oxycodone granules, powdered acetaminophen (APAP), and various excipients including disintegrants, binders, and fillers were charged into the fluid bed granulation device and sprayed with a granulation fluid, resulting in the formation of IR granules in one batch and ER granules in a second batch. The composition of the resulting IR and ER granules are summarized in Table 50.

TABLE 50

Compound	Dry Wt. (% total wt.)	
	IR Layer	ER Layer
Protected oxycodone granules	16.1%	14.2%
APAP	67.8%	81.2%
MCC	5.0%	
Hydroxypropyl cellulose	8.1%	4.5%
Cross carmellose sodium	3.0%	

The IR granules were blended with lubricant excipients in preparation for the tablet pressing process. Similarly, the ER

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particles were blended with various excipients including lubricants, and polyethylene oxide polymer, and a filler in preparation for the tablet pressing process. The compositions of the IR blend and the ER blend are summarized in Table 51 below.

TABLE 51

Compound	Dry Wt. (% total wt.)	
	IR Blend	ER Blend
IR granules	99.25%	
GR granules		52.30%
Silicon dioxide	0.50%	0.50%
Magnesium stearate	0.25%	0.10%
MCC		1.20%
Polyethylene oxide polymer		45.00%

The IR blend and the ER blend were loaded into a bilayer tablet press and formed into bilayer tablets having about 29% of the IR blend and about 71% the ER blend by weight.

A bilayer tablet was manufactured according to the method described in Example 15 according to the formulations in Table 52 (IR portion) and Table 53 (ER portion). The total tablet weight was 1006.5 mg.

TABLE 52

Ingredient	mg/tablet	wt %
Acetaminophen	196.00	67.24
Oxycodone HCl	14.00	4.80
Avicel (within protected granule)	29.67	10.18
Spres B825	1.87	0.64
Citric Acid Anhydrous	0.93	0.32%
EDTA disodium salt, dihydrate	0.17	0.06
Hydroxypropyl cellulose	23.32	8.00
AcDiSol	8.74	3.00
Avicel (as part of IR granule)	14.57	5.00
Silicon Dioxide	1.46	0.50
Mg Stearate	0.73	0.25
Total	291.5	100.0

TABLE 53

Ingredient	mg/tablet	wt %
Acetaminophen	304.00	42.52
Oxycodone HCl	16.00	2.24
Avicel (within protected granule)	33.89	4.74
Spres B825	2.15	0.03
Citric Acid Anhydrous	1.07	0.15
EDTA disodium salt, dihydrate	0.21	0.03
Hydroxypropyl cellulose	16.87	2.36
Polyox	321.75	45.00
Avicel (added to GR blend)	8.37	1.17
Silicon Dioxide	3.58	0.05
Mg Stearate	7.15	1.00
Total	715.0	100.0

In vitro release profiles may be determined for the formulated tablet described above using standard USP Dissolution and Disintegration apparatuses as described in Examples above. In vivo studies to determine

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Example 16

Opioid agonists such as oxycodone have been reported to cause a reduction in motility in the antrum, which results in slowing of gastric emptying (Wood and Galligan, Physicians' Desk Reference, 59th edition (2005) p. 2818). This could affect the erosion time of an extended release gastric retained acetaminophen/opioid combination drug formulation. Preliminary studies were done to determine the effect of oxycodone on erosion time of acetaminophen extended-release tablets comprising a polymer matrix that swells to a size sufficient for retention in the stomach in the fed mode.

This was a randomized 2-way crossover study in 5 healthy female beagle dogs weighing between 12-16 kg to determine the erosion time of acetaminophen gastric retentive extended-release tablets with and without oxycodone administration. Following an overnight fast of at least 14 hours, the dogs were fed 100 g of canned dog food (Pedigree® Traditional ground Dinner with Chunky Chicken).

Fifteen minutes after the animals had consumed the food, the dosage forms were administered. In the oxycodone arm, oxycodone (14 mg in a gelatin capsule (0.28 mL of a 50 mg/mL solution in water)) was administered with the tablet to simulate the immediate-release portion of the proposed formulations. This was followed by a simulated extended-release over the next 4.5 hr (1.8 mg oxycodone in a gelatin capsule (0.036 mL of a 50 mg/mL solution in water) every 30 min for 4.5 hr) for nine doses and a total of 16 mg oxycodone. In addition to the initial feeding the animals were fed another 100 gm of food 4 hours after the first meal. The above procedure was repeated 2 day later with the opposite treatment.

Erosion of the gastric retentive extended-release acetaminophen tablets was assessed using fluoroscopy. Each tablet contained two radio-opaque strings in the shape of an "X". Separation of the strings was considered to signify complete erosion of the tablets. Images were obtained every 30 min until the strings separated. Individual and mean tablet erosion times are presented in Table 35. There was not a significant difference ($p > 0.05$) in erosion time between control and oxycodone.

TABLE 54

Tablet	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Mean \pm SD
Control	4.25 h	4.75 h	4.75 h	4.75 h	4.75 h	4.65 \pm 0.22 h
Oxycodone	6.00 h	5.25 h	5.75 h	5.25 h	4.75 h	5.40 \pm 0.49 h

It was unexpectedly found that the co-administered oxycodone had no significant effect on the erosion time.

Example 17

A study to determine the erosion time of different extended release gastric retentive dosage forms as described herein is done using dogs as a means to predict the drug delivery time in humans. The bilayer tablets containing both the extended release and immediate release components are used in these studies. Each tablet has a total weight of about 1000 mg and contains 500 mg acetaminophen and 15 or 30 mg oxycodone HCl as indicated in Table 36. The gastric retentive (GR) portions of the tablets are formulated according to Example 2 above with the exception of the variations noted in Table 36. The immediate release (IR) layer is formulated according to Example 3 above, except that either hydroxypropyl cellulose or povidone is used as the binder as described in Table 36.

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TABLE 55

Formulation	Oxycodone HCl (mg/tablet)	Polymer (weight percent)	Binder (weight percent)
1 (6 hr release)	15	POLYOX ® N60 K or 301 weight percent ranging from 10 to 55%	GR: PVP, 3 to 15 weight percent IR: PVP or HPC (hydroxypropyl cellulose) 3 to 15 weight percent
2 (8 hr release)	15	POLYOX ® N60 K or 301 weight percent ranging from 15 to 55%	GR: PVP, 3 to 15 weight percent IR: PVP or HPC (hydroxypropyl cellulose) 3 to 15 weight percent
3 (6 hr release)	30	POLYOX ® N60 K or 301 weight percent ranging from 10 to 55%	GR: PVP, 3 to 15 weight percent IR: PVP or HPC (hydroxypropyl cellulose) 3 to 15 weight percent
4 (8 hr release)	30	POLYOX ® N60 K or 301 weight percent ranging from 15 to 55%	GR: PVP, 3 to 15 weight percent IR: PVP or HPC (hydroxypropyl cellulose) 3 to 15 weight percent

A four-way crossover study is carried out in five healthy female beagle dogs. Following an overnight fast of 14 hours, the dogs are fed 100 g canned dog food. Fifteen minutes after the food has been consumed, the dogs are dosed with one of

tablets. Images were obtained every 30 minutes until the strings separated. The erosion results and predicted human erosion times (delivery times) are listed in Table 56 below and illustrated in FIG. 27.

TABLE 56

Dog #	15/500 6 h tablet		15/500 8 hr tablet		30/500 6 hr tablet		30/500 8 hr tablet	
	Dog erosion time (h)	Predicted human erosion time (h)	Dog erosion time (h)	Predicted human erosion time (h)	Dog erosion time (h)	Predicted human erosion time (h)	Dog erosion time (h)	Predicted human erosion time (h)
1	3.25	6.18	7.25	12.18	7.25	12.18	7.75	12.93
2	3.00	5.80	7.25	12.18	4.25	7.68	9.25	15.18
3	5.25	9.18	6.75	11.43	7.25	12.18	8.25	13.68
4	4.75	8.43	6.25	10.68	7.75	12.93	8.75	14.42
5	3.75	6.93	4.75	8.43	6.75	11.43	7.25	12.18
Mean ± SD	4.00 ± 0.97	7.30 ± 1.45	6.45 ± 1.04	10.98 ± 1.56	6.65 ± 1.39	11.28 ± 2.08	8.25 ± 0.79	13.68 ± 1.18

the four formulations to be tested. Four hours after the initial meal, the animals are fed another 100 g of canned dog food.

Erosion of the gastric retentive extended release oxycodone/acetaminophen tablets is assessed using fluoroscopy. Each tablet used in this protocol contains two radio-opaque strings in the shape of an "X." Separation of the strings is considered to signify complete erosion of the tablets. Images are obtained every 30 minutes until the strings separate. The above procedure is repeated at 3-4 day intervals until each dog has been administered four formulations.

Example 18

Erosion studies were carried out to test the erosion times of the tablets containing 500 mg acetaminophen and 15 mg oxycodone HCl as formulated in Tables 35-36 and 38-39 and tablets containing 500 mg acetaminophen and 30 mg oxycodone HCl as formulated in Tables 41-42 and 44-45.

This study was conducted in 5 healthy female beagle dogs weighing between 12-16 kg to determine the erosion time of the bilayer tablets. Following an overnight fast of at least 14 hours, the dogs were fed 100 g of canned dog food (Pedigree® Traditional Ground Dinner with Chunky Chicken). Within 15 minutes of the dog consuming the meal they were administered one of the acetaminophen/oxycodone bilayer tablet formulations. Each dog received each formulation with at least 3 days between administrations. Erosion of the gastric retentive extended-release acetaminophen/oxycodone tablets was assessed using fluoroscopy. Each tablet contained two radio-opaque strings in the shape of an "X." Separation of the strings was considered to signify complete erosion of the

No significant difference was observed between the in vitro erosion times for the 15 mg and 30 mg oxycodone formulation tablets. However, in vivo erosion indicated that oxycodone may have an effect on erosion as the 30 mg tablets had about a 2 hour increase in erosion time as compared to the tablets containing 15 mg oxycodone. Tablets containing 15 mg oxycodone did not appear to have a significant effect on erosion as erosion time for the tablet containing 15 mg oxycodone formulated for 6 hour release was not different from that for the tablet containing acetaminophen only formulated for 6 hour release.

While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

It is claimed:

1. A method for treating pain, comprising: administering at least twice daily, a dosage form comprising an extended release polymer matrix comprising a dose of acetaminophen and a dose of an opioid, wherein the extended release matrix is comprised of a swellable polymer and imbibes fluid after administration to swell to a size sufficient to promote gastric retention of the matrix, wherein the swellable polymer is selected from the group consisting of a polyalkylene oxide, a cellulosic polymer, a poly(acrylamide), a poly(N-vinyl lactam), and a polyvinylamine, and wherein within about 1 hour

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in an in vitro disintegration test the dosage form releases more than about 50% of the dose of acetaminophen, and wherein by about 6 hours in an in vitro disintegration test, the percent of opioid released from the dosage form is greater than the percent of acetaminophen released from the dosage form, and wherein the in vitro disintegration test is at 37° C. in 0.1N HCl.

2. The method of claim 1, wherein substantially all of the doses of acetaminophen and the opioid are released within about ten hours in an in vitro disintegration test.

3. The method of claim 1, wherein the dose of acetaminophen in the dosage form is between about 100-1300 mg.

4. The method of claim 1, wherein the dose of opioid in the dosage form is between about 5-40 mg.

5. The method of claim 4, wherein the dosage form comprises an opioid selected from the group consisting of oxycodone, hydrocodone, and pharmaceutically acceptable salts thereof.

6. The method of claim 3, wherein the dose of opioid in the dosage form is between about 5-40 mg.

7. The method of claim 6, wherein the dosage form comprises an opioid selected from the group consisting of oxycodone, hydrocodone, and pharmaceutically acceptable salts thereof.

8. The method of claim 1, wherein the dosage form comprises an immediate release portion.

9. The method of claim 7, wherein the dosage form comprises an immediate release portion.

10. The method of claim 9, wherein the dosage form comprises between about 20-50 weight percent of poly(ethylene oxide).

11. The method of claim 10, wherein the poly(ethylene oxide) has a molecular weight of between about 900,000 Daltons to about 4,000,000 Daltons.

12. The method of claim 1, wherein the dosage form comprises between about 20-50 weight percent of poly(ethylene oxide).

13. The method of claim 12, wherein the poly(ethylene oxide) has a molecular weight of between about 900,000 Daltons to about 2,000,000 Daltons.

14. A method for treating pain, comprising: administering at least twice daily, a dosage form comprising

an extended release polymer matrix comprising a dose of acetaminophen and a dose of an opioid, wherein the extended release matrix (i) is comprised of a swellable polymer and (ii) imbibes fluid after administration to swell to a size sufficient to promote gastric retention of the matrix, wherein the swellable polymer is selected from the group consisting of a polyalkylene oxide, a cellulosic polymer, a poly(acrylamide), a poly(N-vinyl lactam), and a polyvinylamine, and wherein at about 1 hour in an in vitro disintegration test the percent of acetaminophen released by the dosage form is greater than the percent of opioid released, and wherein by about 4-6 hours in an in vitro disintegration test, the dosage form releases greater than 90% of the dose of acetaminophen and the cumulative percent of opioid released is within about 10% of the cumulative percent of acetaminophen released, and wherein the in vitro disintegration test is at 37° C. in 0.1N HCl.

15. The method of claim 14, wherein substantially all of the doses of acetaminophen and the opioid are released within about ten hours in an in vitro disintegration test.

16. The method of claim 14, wherein the dose of acetaminophen in the dosage form is between about 100-1300 mg.

17. The method of claim 14, wherein the dose of opioid in the dosage form is between about 5-40 mg.

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18. The method of claim 17, wherein the dosage form comprises an opioid selected from the group consisting of oxycodone, hydrocodone, and pharmaceutically acceptable salts thereof.

19. The method of claim 16, wherein the dose of opioid in the dosage form is between about 5-40 mg.

20. The method of claim 19, wherein the dosage form comprises an opioid selected from the group consisting of oxycodone, hydrocodone, and pharmaceutically acceptable salts thereof.

21. The method of claim 14, wherein the dosage form comprises an immediate release portion.

22. The method of claim 20, wherein the dosage form comprises an immediate release portion.

23. The method of claim 22, wherein the dosage form comprises between about 20-50 weight percent of poly(ethylene oxide).

24. The method of claim 23, wherein the poly(ethylene oxide) has a molecular weight of between about 900,000 Daltons to about 4,000,000 Daltons.

25. The method of claim 14, wherein the dosage form comprises between about 20-50 weight percent of poly(ethylene oxide).

26. The method of claim 25, wherein the poly(ethylene oxide) has a molecular weight of between about 900,000 Daltons to about 2,000,000 Daltons.

27. A method for treating pain, comprising: administering at least twice daily, a dosage form comprising

an extended release polymer matrix comprising a dose of acetaminophen and a dose of an opioid, wherein the extended release matrix (i) is comprised of a swellable polymer and (ii) imbibes fluid after administration to swell to a size sufficient to promote gastric retention of the matrix, wherein the swellable polymer is selected from the group consisting of a polyalkylene oxide, a cellulosic polymer, a poly(acrylamide), a poly(N-vinyl lactam), and a polyvinylamine, and wherein in an in vitro disintegration test the percent of acetaminophen released is greater than the percent of opioid released at times of 3 hours or less, at times greater than about 6 hours, the percent of opioid released is greater than the percent of acetaminophen released, and wherein the in vitro disintegration test is at 37° C. in 0.1N HCl.

28. The method of claim 27, wherein substantially all of the doses of acetaminophen and the opioid are released within about ten hours in an in vitro disintegration test.

29. The method of claim 27, wherein the dose of acetaminophen in the dosage form is between about 100-1300 mg.

30. The method of claim 27, wherein the dose of opioid in the dosage form is between about 5-40 mg.

31. The method of claim 30, wherein the dosage form comprises an opioid selected from the group consisting of oxycodone, hydrocodone, and pharmaceutically acceptable salts thereof.

32. The method of claim 29, wherein the dose of opioid in the dosage form is between about 5-40 mg.

33. The method of claim 32, wherein the dosage form comprises an opioid selected from the group consisting of oxycodone, hydrocodone, and pharmaceutically acceptable salts thereof.

34. The method of claim 27, wherein the dosage form comprises an immediate release portion.

35. The method of claim 33, wherein the dosage form comprises an immediate release portion.

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36. The method of claim 35, wherein the dosage form comprises between about 20-50 weight percent of poly(ethylene oxide).

37. The method of claim 36, wherein the poly(ethylene oxide) has a molecular weight of between about 900,000 Daltons to about 4,000,000 Daltons.

38. The method of claim 27, wherein the dosage form comprises between about 20-50 weight percent of poly(ethylene oxide).

39. The method of claim 38, wherein the poly(ethylene oxide) has a molecular weight of between about 900,000 Daltons to about 2,000,000 Daltons.

40. The method of claim 1, wherein the swellable polymer is an alkyl-substituted cellulosic polymer or a polyalkylene oxide.

41. The method of claim 14, wherein the swellable polymer is an alkyl-substituted cellulosic polymer or a polyalkylene oxide.

42. The method of claim 27, wherein the swellable polymer is an alkyl-substituted cellulosic polymer or a polyalkylene oxide.

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